EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	4	(pan.in. or roczniak.in.) and VPAC1	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2007/02/27 13:47
L2	1	r2p16	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2007/02/27 13:47
L3	34	vpac1 same antagonist	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2007/02/27 13:48
L4	6	VIP same GHRH same fusion	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2007/02/27 13:48

```
Welcome to DIALOG

Dialog level 05.16.01D
? b 411;set files biotech
     27feb07 13:50:34 User219511 Session D677.2
        $0.00   0.117 DialUnits File410
    $0.00  Estimated cost File410
    $0.02  TELNET
    $0.02  Estimated cost this search
    $0.49  Estimated total session cost   0.253 DialUnits
File 411:DIALINDEX(R)

DIALINDEX(R)
  (c) 2007 Dialog

*** DIALINDEX search results display in an abbreviated ***
*** format unless you enter the SET DETAIL ON command. ***
  You have 26 files in your file list.
  (To see banners, use SHOW FILES command)
? s vpac1 and antagonist

Your SELECT statement is:
  s vpac1 and antagonist

      Items  File
      -----  ----
         49    5: Biosis Previews(R)_1969-2007/Feb W3
          2   24: CSA Life Sciences Abstracts_1966-2007/Nov
         17   34: SciSearch(R) Cited Ref Sci_1990-2007/Feb W3
         13   71: ELSEVIER BIOBASE_1994-2007/Feb W3
         23   73: EMBASE_1974-2007/Feb 27
          1   94: JICST-EPlus_1985-2007/Mar W1
          1   98: General Sci Abs_1984-2007/Feb
          7  135: NewsRx Weekly Reports_1995-2007/Feb W3
         12  144: Pascal_1973-2007/Feb W3
         33  155: MEDLINE(R)_1950-2007/Feb 23
          1  357: Derwent Biotech Res.__1982-2007/Feb W3
          7  399: CA SEARCH(R)_1967-2007/UD=14610

  12 files have one or more items; file list includes 26 files.

? s vpac1 and antagonist?

Your SELECT statement is:
  s vpac1 and antagonist?

      Items  File
      -----  ----
         67    5: Biosis Previews(R)_1969-2007/Feb W3
          4   24: CSA Life Sciences Abstracts_1966-2007/Nov
         25   34: SciSearch(R) Cited Ref Sci_1990-2007/Feb W3
         19   71: ELSEVIER BIOBASE_1994-2007/Feb W3
         28   73: EMBASE_1974-2007/Feb 27
          2   94: JICST-EPlus_1985-2007/Mar W1
          4   98: General Sci Abs_1984-2007/Feb
          8  135: NewsRx Weekly Reports_1995-2007/Feb W3
         15  144: Pascal_1973-2007/Feb W3
         65  155: MEDLINE(R)_1950-2007/Feb 23
          1  357: Derwent Biotech Res.__1982-2007/Feb W3
          8  399: CA SEARCH(R)_1967-2007/UD=14610

  12 files have one or more items; file list includes 26 files.

? s (vpac1 and antagonist?) or r2p16

Your SELECT statement is:
  s (vpac1 and antagonist?) or r2p16

      Items  File
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         67    5: Biosis Previews(R)_1969-2007/Feb W3
          4   24: CSA Life Sciences Abstracts_1966-2007/Nov
         25   34: SciSearch(R) Cited Ref Sci_1990-2007/Feb W3
         19   71: ELSEVIER BIOBASE_1994-2007/Feb W3
         28   73: EMBASE_1974-2007/Feb 27
          2   94: JICST-EPlus_1985-2007/Mar W1
          4   98: General Sci Abs_1984-2007/Feb
          8  135: NewsRx Weekly Reports_1995-2007/Feb W3
         15  144: Pascal_1973-2007/Feb W3
         65  155: MEDLINE(R)_1950-2007/Feb 23
          1  357: Derwent Biotech Res.__1982-2007/Feb W3
          8  399: CA SEARCH(R)_1967-2007/UD=14610

  12 files have one or more items; file list includes 26 files.

? save temp; b 155,5,24,34,71,73,94,98,135,144,357,399;exs;rd
Temp SearchSave "TG383297582" stored
     27feb07 13:51:38 User219511 Session D677.3
        $3.08   1.047 DialUnits File411
    $3.08  Estimated cost File411
    $0.53  TELNET
    $3.61  Estimated cost this search
    $4.10  Estimated total session cost   1.299 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R) 1950-2007/Feb 23
       (c) format only 2007 Dialog
  File   5:Biosis Previews(R) 1969-2007/Feb W3
       (c) 2007 The Thomson Corporation
*File   5: In preparation for coming enhancements, accession numbers will
change soon. See HELP NEWS 5 for details.
  File  24:CSA Life Sciences Abstracts 1966-2007/Nov
       (c) 2007 CSA.
  File  34:SciSearch(R) Cited Ref Sci 1990-2007/Feb W3
       (c) 2007 The Thomson Corp
  File  71:ELSEVIER BIOBASE 1994-2007/Feb W3
       (c) 2007 Elsevier B.V.
  File  73:EMBASE 1974-2007/Feb 27
       (c) 2007 Elsevier B.V.
  File  94:JICST-EPlus 1985-2007/Mar W1
       (c)2007 Japan Science and Tech Corp(JST)
*File  94: UD200609W2 is the last update for 2006. UD200701W1 is the
first update for 2007. The file is complete and up to date.
  File  98:General Sci Abs 1984-2007/Feb
       (c) 2007 The HW Wilson Co.
  File 135:NewsRx Weekly Reports 1995-2007/Feb W3
       (c) 2007 NewsRx
  File 144:Pascal 1973-2007/Feb W3
       (c) 2007 INIST/CNRS
  File 357:Derwent Biotech Res. _1982-2007/Feb W3
       (c) 2007 The Thomson Corp.
  File 399:CA SEARCH(R) 1967-2007/UD=14610
       (c) 2007 American Chemical Society
*File 399: Use is subject to the terms of your user/customer agreement.
IPCR/8 classification codes now searchable as IC=. See HELP NEWSIPCR.

    Set  Items  Description
    ---  -----  -----------
Executing TG383297582
Hilight option is not available in file(s) 399
HILIGHT set on as '%'
         1028  VPAC1
      1686589  ANTAGONIST?
            0  R2P16
    S1    246  (VPAC1 AND ANTAGONIST?) OR R2P16
    S2    119  RD  (unique items)
? t s2/7/1-119;bye

 2/7/1    (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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22839879 PMID: 16962672
Novel extended and branched N-terminal analogs of VIP.
Dangoor David; Rubinraut Sara; Fridkin Mati; Gozes Illana
Department of Human Molecular Genetics and Biochemistry, Sackler School of Medicine, Tel Aviv University, Einstein Street, Tel Aviv 69978, Israel.
Regulatory peptides (Netherlands) Nov 15 2006, 137 (1-2) p42-9, ISSN 0167-0115--Print Journal Code: 8100479
Publishing Model Print-Electronic
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The effects of vasoactive intestinal peptide (VIP) are primarily mediated through %VPAC1% and VPAC2, receptors that are preferentially coupled to adenylate cyclase activation. As a large majority of the potent VIP %antagonists% have modifications in the N-terminal domain of the peptide, the effect of multiplication of this domain on VIP was examined with the aim of possibly amplifying peptide-receptor (%VPAC1%) activation. Several VIP analogs were designed and synthesized, each carrying multiplication of the N-terminal domain that was obtained by either linear tandem extension or by parallel branching. Circular dichorism (CD) analysis revealed that these extended/branched peptides maintained an alpha helical structure in organic environment, similar to VIP. A specific branched VIP analog was found to be slightly more potent towards %VPAC1%-related cAMP production as compared to VIP. This analog could have potential therapeutic value in several disorders, similar to VIP. Two branched N-terminal VIP sequences demonstrated superior receptor binding and activation as compared to two N-terminals in tandem. The results suggest that correct alignment of the VIP N-terminal region is important for receptor binding and activation. However, increased receptor binding was not directly associated with increased cAMP production suggesting steric dynamic interactions.
Record Date Created: 20061122
Record Date Completed: 20070213
Date of Electronic Publication: 20060908

2/7/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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22793826 PMID: 16650965
Asn229 in the third helix of %VPAC1% receptor is essential for receptor activation but not for receptor phosphorylation and internalization: comparison with Asn216 in VPAC2 receptor.
Nachtergael Ingrid; Gaspard Nathalie; Langlet Christelle; Robberecht Patrick; Langer Ingrid
Department of Biological Chemistry and Nutrition, Faculty of Medicine, Universite Libre de Bruxelles, Belgium.
Cellular signalling (England) Dec 2006, 18 (12) p2121-30, ISSN 0898-6568--Print Journal Code: 8904683
Publishing Model Print-Electronic
Document type: Comparative Study; Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
After stimulation with agonist, G protein coupled receptors (GPCR) undergo conformational changes that allow activation of G proteins to transduce the signal, followed by phosphorylation by kinases and arrestin binding to promote receptor internalization. Actual paradigm, based on a study of GPCR-A/rhodopsin family, suggests that a network of interactions between conserved residues located in transmembrane (TM) domains (mainly TM3, TM6 and TM7) is involved in the molecular switch leading to GPCR activation. We evaluated in CHO cells expressing the VPAC(1) receptor the role of the third transmembrane helix in agonist signalling by point mutation into Ala of the residues highly conserved in the secretin-family of receptors: Y(224), N(229), F(230), W(232), E(236), G(237), Y(239), L(240). N(229)A VPAC(1) mutant was characterized by a decrease in both potency and efficacy of VIP stimulated adenylate cyclase activity, by the absence of agonist stimulated [Ca(2+)](i) increase, by a preserved receptor recognition of agonists and %antagonist% and by a preserved sensitivity to GTP suggesting the importance of that residue for efficient G protein activation. N(229)D mutant was not expressed at the membrane, and the N(229)Q with a conserved mutation was less affected than the A mutant. Agonist stimulated phosphorylation and internalization of N(229)A and N(229)Q VPAC(1) were unaffected. However, the re-expression of internalized mutant receptors, but not that of the wild type receptor, was rapidly reversed after VIP washing. Receptor phosphorylation, internalization and re-expression may be thus dissociated from G protein activation and linked to another active conformation that may influence its trafficking. Mutation of that conserved amino acid in VPAC(2) could be investigated only by a conservative mutation (N(216)Q) and led to a receptor with a low VIP stimulation of adenylate cyclase, receptor phosphorylation and internalization. This indicated the importance of the conserved N residue in the TM3 of that family of receptors.
Record Date Created: 20061031
Record Date Completed: 20070205
Date of Electronic Publication: 20060327

2/7/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2007 Dialog. All rts. reserv.

22696782 PMID: 16901992
Identification of key residues that cause differential gallbladder response to PACAP and VIP in the guinea pig.
Wei Muxin; Fujiki Kotoyo; Ando Eiji; Zhang Sumin; Ozaki Tsuyoshi; Ishiguro Hiroshi; Kondo Takaharu; Nokihara Kiyoshi; Wray Victor; Naruse Satoru
The First Affiliated Hospital of Nanjing Medical University, Nanjing, China.
American journal of physiology. Gastrointestinal and liver physiology (United States) Jan 2007, 292 (1) pG76-83, ISSN 0193-1857--Print Journal Code: 100901227
Publishing Model Print-Electronic
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
Pituitary adenylate cyclase-activating polypeptide (PACAP) and vasoactive intestinal polypeptide (VIP) have opposite actions on the gallbladder; PACAP induces contraction, whereas VIP induces relaxation. Here, we have attempted to identify key residues responsible for their interactions with PACAP (PAC1) and VIP (VPAC) receptors in the guinea pig gallbladder. We synthesized PACAP-27/VIP hybrid peptides and compared their actions on isolated guinea pig gallbladder smooth muscle strips using isotonic transducers. [Ala4]- and [Val5]PACAP-27 were more potent than PACAP-27 in stimulating the gallbladder. In contrast, [Ala4, Val5]- and [Ala4, Val5, Asn9]PACAP-27 induced relaxation similarly to VIP. [Asn9]-, [Thr11]-, or [Leu13]PACAP-27 had 20-70% contractile activity of PACAP-27, whereas [Asn24,Ser25,Ile26]PACAP-27 showed no change in the activity. All VIP analogs, including [Gly4,Ile5,Ser9]VIP, induced relaxation. In the presence of a PAC1 receptor %antagonist%, PACAP(6-38), the contractile response to PACAP-27 was inhibited and relaxation became evident. RT-PCR analysis revealed abundant expressions of PAC1 receptor, "hop" splice variant, and %VPAC1% and VPAC2 receptor mRNAs in the guinea pig gallbladder. In conclusion, PACAP-27 induces contraction of the gallbladder via PAC1/hop receptors. Gly4 and Ile5 are the key NH2-terminal residues of PACAP-27 that distinguish PAC1/hop receptors from %VPAC1%/VPAC2 receptors. However, both the NH2-terminal and alpha-helical regions of PACAP-27 are required for initiating gallbladder contraction.
Record Date Created: 20070111
Date of Electronic Publication: 20060810

2/7/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

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22594924 PMID: 17030371
Mechanisms of vasoactive intestinal peptide-elicited coronary vasodilation in the isolated perfused rat heart.
Sawmiller Darrell R; Ashtari Mozhgan; Urueta Hedy; Leschinsky Melissa; Henning Robert J
Department of Internal Medicine/Cardiology, University of South Florida Health Science Center, Tampa, FL 33612-4799, USA. dsawmill@hsc.usf.edu
Neuropeptides (Scotland) Oct 2006, 40 (5) p349-55, ISSN 0143-4179--Print Journal Code: 8103156
Publishing Model Print-Electronic
Document type: In Vitro; Journal Article; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, Non-P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The present study investigated the potential role of vasoactive intestinal peptide (VIP) receptors, %VPAC1% and VPAC2, in VIP-elicited coronary vasodilation of the isolated perfused rat heart. Additional studies determined the role of ATP-sensitive (K(ATP)) and voltage-gated K(+) (K(V)) channels in the VIP-elicited coronary vasodilation. Both the selective %VPAC1% agonist, K15,R16,L27VIPI-7GRF8-27, and the selective VPAC2 agonist, RO25-1553, decreased coronary vascular resistance (CVR) in a dose-dependent manner, with EC(50) values of 1.67x10(-9)M and 7.11x10(-9)M, respectively (%VPAC1% vs VPAC2 agonist, P<0.05). K15,R16,L27VIP1-7GRF8-27 and RO25-1553 maximally reduced CVR by -42+/-4% and -39+/-6% at 1x10(-8) and 3x10(-8)M, respectively. VIP at 1x10(-10)M decreased CVR by -14+/-2% in the absence (vehicle), by -11+/-3% in the presence of the nonselective VIP receptor %antagonist% VIP10-28 (1x10(-7)M; P>0.05 vs. vehicle) and by only -4+/-2% in the presence of the selective VPAC2 receptor %antagonist% PACAP6-38 (1x10(-7)M; P<0.05 vs. vehicle). In additional studies, VIP at 1x10(-10)M decreased CVR by -22+/-1% in the absence (control) and by only -10+/-2% in the presence of the nonselective K(+) channel blocker tetrabutylammonium (3x10(-4)M; P<0.05 vs. control). VIP reduced CVR by -4+/-1% in the presence of the K(ATP) channel blocker glibenclamide (3x10(-6)M; P<0.05 vs control) and by -28+/-2% in the presence of the K(V) channel blocker 4-aminopyridine (3x10(-4)M; P>0.05 vs control). Thus, selective %VPAC1% and VPAC2 receptor activation in the coronary circulation produces vasodilation and the VIP-elicited coronary vasodilation involves activation of VPAC2 receptors and K(ATP) but not K(V) channels. In addition, VIP10-28 does not effectively block coronary vascular VIP receptors.
Record Date Created: 20061030
Record Date Completed: 20070104
Date of Electronic Publication: 20061009

2/7/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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22518214 PMID: 16965837
Vasoactive intestinal peptide enhances wound healing and proliferation of human bronchial epithelial cells.
Guan Cha-Xiang; Zhang Min; Qin Xiao-Qun; Cui Yan-Ru; Luo Zi-Qiang; Bai Hong-Bo; Fang Xiang
Department of Physiology, Central South University Xiangya Medical School, Changsha, Hunan 410078, China.
Peptides (United States) Dec 2006, 27 (12) p3107-14, ISSN 0196-9781--Print Journal Code: 8008690
Publishing Model Print-Electronic
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
In the present study, we investigated the effects of vasoactive intestinal peptide (VIP) on wound healing of bronchial epithelium. Wound healing of the mechanical damaged human bronchial epithelial cells (HBEC) was observed in the absence or presence of VIP. Effects of VIP on chemotactic migration, cell proliferation of HBEC were also tested. HBEC chemotaxis was assessed by the blind well chamber technique, the cell cycle was determined by flow cytometry, and cell proliferation was determined by measuring the expression of proliferating cell nuclear antigen Ki67. Effects of VIP on epithelial E-cadherins protein and mRNA were also measured by immunohistochemistry and RT-PCR. The results showed that VIP accelerated the recovery of wound area of HBEC. VIP increased the migration and proliferation of HBEC, and these effects were blocked by a %VPAC1% receptor %antagonist% . VIP also increased the expression of E-cadherin mRNA and protein in HBEC, suggesting that protective effects of VIP on wound healing may be related to its ability to increase the expression of E-cadherin. In conclusion, VIP has protective effects against human bronchial epithelial cell damage, and the beneficial effects of VIP might be mediated, at least in part, by %VPAC1%, and associated with increased expression of E-cadherin. .
Record Date Created: 20061120
Date of Electronic Publication: 20060911

2/7/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2007 Dialog. All rts. reserv.

22472165 PMID: 17056516
Human plasmacytoid dendritic cell function: inhibition of IFN-alpha secretion and modulation of immune phenotype by vasoactive intestinal peptide.
Fabricius Dorit; O'Dorisio M Sue; Blackwell Sue; Jahrsdorfer Bernd
Department of Pediatrics, Holden Comprehensive Cancer Center, Carver College of Medicine, University of Iowa, Iowa City, IA 52242, USA.
Journal of immunology (Baltimore, Md. - 1950) (United States) Nov 1 2006, 177 (9) p5920-7, ISSN 0022-1767--Print Journal Code: 2985117R
Contract/Grant No.: R01 CA 82691; CA; NCI
Publishing Model Print
Document type: Journal Article; Research Support, N.I.H., Extramural; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Plasmacytoid dendritic cells (PDC) are considered the main sentinels against viral infections and play a major role in immune tolerance. Vasoactive intestinal peptide (VIP) is a potent immunomodulator, whose role in PDC function is unknown. The present study was designed to investigate whether human PDC express VIP receptors and whether VIP has immunological effects on PDC. Using real-time RT-PCR and immunofluorescence, we demonstrated that VIP receptors %VPAC1% and VPAC2 are expressed on PDC. After culturing PDC with VIP and CpG oligodeoxynucleotides for 48 h, expression of surface molecules with significance for PDC-T cell interactions as well as IFN-alpha secretion were quantified using FACS analysis and ELISA, respectively. For functional assays, CFSE-stained CD4+ T cells were coincubated with differentially treated PDC. T cell proliferation and production of various cytokines were determined by FACS analysis and ELISA. VIP enhanced PDC expression of CD86, MHC II, and CCR7. In contrast, VIP inhibited PDC secretion of IFN-alpha and expression of Neuropilin-1 and MHC I. The potential of CpG oligodeoxynucleotide-activated PDC to induce proliferation of allogeneic CD4(+) T cells was impaired when VIP was present during activation. Furthermore, pretreatment of PDC with VIP resulted in a decrease of the IFN-gamma:IL-4 ratio in cocultured T cells, suggesting a modulation of the immune response toward Th2. Taken together, these results strongly suggest that VIP regulates the immunological function of human PDC. VIP may thus be involved in the modulation of immune responses to viral infections as well as in the maintenance of immune tolerance.
Record Date Created: 20061023
Record Date Completed: 20061213

2/7/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2007 Dialog. All rts. reserv.

22356419 PMID: 16905223
VIP provides cellular protection through a specific splice variant of the PACAP receptor: a new neuroprotection target.
Pilzer Inbar; Gozes Illana
Department of Human Molecular Genetics and Biochemistry, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv 69978, Israel.
Peptides (United States) Nov 2006, 27 (11) p2867-76, ISSN 0196-9781 --Print Journal Code: 8008690
Publishing Model Print-Electronic
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
Vasoactive intestinal peptide (VIP) was known to provide neuroprotection. Three VIP receptors have been cloned: %VPAC1%, VPAC2 and PAC1. A specific splice variant of PAC1 in the third cytoplasmatic loop, hop2, was implicated in VIP-related neuroprotection. We aimed to clone the hop2 splice variant, examine its affinity to VIP and investigate whether it mediates the VIP-related neuroprotective activity. The PAC1 cDNA was cloned from rat cerebral astrocytes. Using genetic manipulation the hop2 splice variant was obtained, then inserted into an expression vector and transfected into COS-7 cells that were used for binding assays. Results showed that VIP bound the cloned hop2 splice variant. Stearyl-neurotensin(6-11) VIP(7-28) (SNH), an %antagonist% for VIP, was also found to bind hop2. In addition, VIP protected COS-7 cells expressing hop2 from oxidative stress. Parallel assays demonstrated that VIP increased cAMP accumulation in COS-7 cells expressing hop2. These results support the hypothesis that hop2 mediates the cytoprotective effects attributed to VIP.
Record Date Created: 20061023
Date of Electronic Publication: 20060814

2/7/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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21702845 PMID: 16564114
Signaling involved in pituitary adenylate cyclase-activating polypeptide-stimulated ADNP expression.
Nakamachi Tomoya; Li Min; Shioda Seiji; Arimura Akira
U.S.-Japan Biomedical Research Laboratories, Department of Medicine, Tulane University School of Medicine, New Orleans, LA 70112, USA.
Peptides (United States) Jul 2006, 27 (7) p1859-64, ISSN 0196-9781 --Print Journal Code: 8008690
Publishing Model Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Activity-dependent neurotrophic protein (ADNP) was discovered as a novel response gene for VIP and has neuroprotective potential. When the VIP paralog, PACAP38 was added to mouse neuron-glia co-cultures, it induced ADNP mRNA expression in a bimodal fashion at subpico- and nanomolar concentrations with greater response at subpicomolar level. The response was attenuated by a PAC1-R %antagonist% at both concentrations and by a %VPAC1%-R %antagonist% at nanomolar concentration only. An IP3/PLC inhibitor attenuated the response at both concentrations of PACAP38, but a MAPK inhibitor had no effect. A PKA inhibitor suppressed the response at nanomolar concentration only. These findings suggest that ADNP expression is mediated through multiple receptors and signaling pathways that are regulated by different concentrations of PACAP.
Record Date Created: 20060619
Record Date Completed: 20060928
Date of Electronic Publication: 20060324

2/7/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2007 Dialog. All rts. reserv.

21223296 PMID: 16566916
Neurogenic secretion mediated by the purinergic P2Y1 receptor in guinea-pig small intestine.
Fang Xiucai; Hu Hong-Zhen; Gao Na; Liu Sumei; Wang Guo-Du; Wang Xi-Yu; Xia Yun; Wood Jackie D
Department of Physiology and Cell Biology, College of Medicine and Public Health, The Ohio State University, 304 Hamilton Hall, 1645 Neil Avenue, Columbus, OH 43210-1218, USA.
European journal of pharmacology (Netherlands) Apr 24 2006, 536 (1-2) p113-22, ISSN 0014-2999--Print Journal Code: 1254354
Contract/Grant No.: KO8 DK60468; DK; NIDDK; R01 DK 37238; DK; NIDDK; R01 DK 68258; DK; NIDDK
Publishing Model Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
We tested the hypothesis that ATP is an enteric neurotransmitter that acts at P2Y1 excitatory purinergic receptors on intestinal secretomotor neurons to evoke neurogenic mucosal secretion in the guinea pig. Ussing chamber methods for studying neurogenic intestinal secretion were used to test the hypothesis. Application of ATP evoked concentration-dependent increases in short circuit current (Isc) indicative of stimulation of electrolyte secretion. MRS2179, a selective P2Y1 purinergic receptor %antagonist% , suppressed the ATP-evoked responses in a concentration-dependent manner with an IC50 of 0.9+/-0.1 microM. Tetrodotoxin or a selective vasoactive intestinal peptide (%VPAC1%) receptor %antagonist% suppressed or abolished the ATP-evoked responses. A selective %VPAC1% receptor %antagonist% also suppressed Isc responses evoked by electrical field stimulation of the secretomotor neurons. Secretory responses to ATP were not suppressed by scopolamine, piroxicam nor selective adenosine receptor %antagonists%. Region-specific differences in responses to ATP corresponded to regional differences in the expression of mRNA transcripts for the P2Y1 receptor. Post-receptor signal transduction for the P2Y1-evoked responses involved stimulation of phospholipase C and an IP3/Ca2+-calmodulin/protein kinase C signaling cascade. Our evidence suggests that ATP is released as a neurotransmitter to stimulate neurogenic mucosal secretion by binding to P2Y1 receptors expressed by VIP-ergic secretomotor neurons.
Record Date Created: 20060417
Record Date Completed: 20060725
Date of Electronic Publication: 20060228

2/7/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2007 Dialog. All rts. reserv.

20638924 PMID: 15959462
Location and function of %VPAC1% , VPAC2 and NPR-C receptors in VIP-induced vasodilation of porcine basilar arteries.
Grant Stuart; Lutz Eve M; McPhaden Alan R; Wadsworth Roger M
Department of Physiology and Pharmacology, University of Strathclyde, Glasgow, Scotland, UK.
Journal of cerebral blood flow and metabolism - official journal of the International Society of Cerebral Blood Flow and Metabolism (United States) Jan 2006, 26 (1) p58-67, ISSN 0271-678X--Print Journal Code: 8112566
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Vasoactive intestinal peptide (VIP) is a vasodilator peptide present in cerebrovascular nerves. Vasoactive intestinal peptide can activate %VPAC1%, VPAC2 and the NPR-C receptor. This study sought to determine the receptors involved in VIP-induced vasodilation of porcine basilar arteries. Porcine basilar arteries contained the messenger ribonucleic acid of all three receptors. Immunocytochemical analysis of porcine basilar arteries revealed

that the %VPAC1% receptor is expressed on the endothelium, VPAC2 on the outer layers of the media and the NPR-C receptor throughout the artery, including nerves. Vasodilator responses to all receptor agonists showed that the receptors are functional. The vasodilator response to the %VPAC1% receptor agonist was inhibited by L-NAME and abolished by endothelial denudation. Vasodilation induced by Ro-25-1553, the VPAC2 agonist, was unaffected by NOS inhibition or removal of the endothelium. Activation of the NPR-C receptor produced a vasodilation, which was susceptible to NOS inhibition and independent of endothelium. The vasodilator response to electrical stimulation at 20 Hz was attenuated by PG-99-465, the VPAC2 %antagonist%. This study shows that all known VIP receptors are involved in VIP-mediated vasodilation of porcine basilar arteries. The %VPAC1% receptor is located on the endothelium and elicits vasodilation by generating nitric oxide (NO). The VPAC2 receptor is mainly expressed in the outer layers of the smooth muscle and induces vasodilation independently of NO in response to VIP released from intramural nerves. The NPR-C receptor produces NO-dependent vasodilation independently of the endothelium by stimulation of nNOS in intramural nerves.
Record Date Created: 20051221
Record Date Completed: 20060503

2/7/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

19553224 PMID: 15976009
PAC1 receptors mediate pituitary adenylate cyclase-activating polypeptide- and progesterone-facilitated receptivity in female rats.
Apostolakis Ede Marie; Riherd Deanna N; O'Malley Bert W
Department of Molecular and Cell Biology, Baylor College of Medicine, One Baylor Plaza, Houston, Texas 77030, USA. edea@bcm.tmc.edu
Molecular endocrinology (Baltimore, Md.) (United States) Nov 2005, 19 (11) p2798-811, ISSN 0888-8809--Print Journal Code: 8801431
Contract/Grant No.: HD42252; HD; NICHD; U54 HD07495; HD; NICHD
Publishing Model Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Pituitary adenylate cyclase-activating polypeptide (PACAP) acts as a feed-forward, paracrine/autocrine factor in the hypothalamic ventromedial nucleus (VMN) for receptivity and sensitizes pituitary hormone release for ovulation. The present study examined receptor(s) and signaling pathway by which PACAP enhances rodent lordosis. PACAP binds to PACAP (PAC1)- and vasoactive intestinal peptide-preferring receptors (%VPAC1% , VPAC2). Ovariectomized rodents primed with estradiol (EB) were given PACAP or vasoactive intestinal peptide directly onto VMN cells. Only PACAP facilitated receptivity. Pretreatment with %VPAC1% and VPAC2 inhibitors blocked both PACAP- and progesterone (P)-induced receptivity. Antisense (AS) oligonucleotides to PAC1 (not %VPAC1% or VPAC2) inhibited the behavioral effect of PACAP and P. By real-time RT-PCR, EB, P and EB+P enhanced VMN mRNA expression of PAC1. Within the total PAC1 population, EB and EB+P induced expression of short form PAC1 and PAC1hop2 splice variants. Finally, blocking cAMP/protein kinase A signaling cascade by %antagonists% to cAMP activity and protein kinase A or by antisense to dopamine- and cAMP-regulated phosphoprotein of 32 kDa blocked the PACAP effect on behavior. Collectively, these findings provide evidence that progesterone receptor-dependent receptivity is, in part, dependent on PAC1 receptors for intracellular VMN signaling and delineate a novel, steroid-dependent mechanism for a feed-forward reinforcement of steroid receptor-dependent reproductive receptivity.
Record Date Created: 20051026
Record Date Completed: 20051213
Date of Electronic Publication: 20050623

2/7/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

15540712 PMID: 16019382
Pituitary adenylate cyclase-activating peptide/vasoactive intestinal peptide receptors in human normal mammary gland and breast cancer tissue.
Garcia-Fernandez M Olga; Collado Beatriz; Bodega Guillermo; Cortes Joaquin; Ruiz-Villaespesa Antonio; Carmena Maria J; Prieto Juan Carlos
Department of Biochemistry and Molecular Biology, University of Alcala, E-28871 Alcala de Henares, Spain.
Gynecological endocrinology - the official journal of the International Society of Gynecological Endocrinology (England) Jun 2005, 20 (6) p327-33, ISSN 0951-3590--Print Journal Code: 8807913
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating peptide (PACAP) bind similarly to %VPAC1% and VPAC2 receptors, whereas PACAP binds with higher affinity than VIP to PAC1 receptors. Here we demonstrate by different approaches the expression of the three subclasses of PACAP/VIP receptors in human normal and malignant breast tissue. At the mRNA level, reverse transcription-polymerase chain reaction experiments showed %VPAC1% and VPAC2 receptors as well as various isoforms (null, hip/hop) of PAC1 receptors due to alternative splicing. At the protein level, Western blot experiments revealed the three subclasses of receptor although no conclusive differences could be established when comparing control, peritumoral and tumoral tissue samples. Immunohistochemistry showed the distribution of these receptors: they were located at epithelial cells in normal and cancer conditions but also in leukocytes at the stromal level in carcinomatous tissue. A weaker immunostaining of PAC1 receptors in normal tissue and a strong density of the three PACAP/VIP receptor subclasses in cancer tissue may be related to differential expression patterns during breast tumor progression but more samples need to be studied to validate this hypothesis. PAC1, %VPAC1% and VPAC2 receptors were functional, as shown by their coupling to adenylate cyclase stimulation: VIP, PACAP-27 and PACAP-38 behaved similarly at this level, whereas both VPAC receptors acted alike as shown by means of specific peptide agonists and %antagonists%. The present results together with the known presence of PACAP and VIP in the mammary gland support a paracrine/autocrine involvement of both peptides at this level in physiological and pathological conditions, i.e. during malignant transformation.
Record Date Created: 20050715
Record Date Completed: 20051020

2/7/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

15507089 PMID: 15935995
VIP enhances synaptic transmission to hippocampal CA1 pyramidal cells through activation of both %VPAC1% and VPAC2 receptors.
Cunha-Reis Diana; Ribeiro Joaquim Alexandre; Sebastiao Ana M
Institute of Pharmacology and Neurosciences, Faculty of Medicine, University of Lisbon, Av. Prof. Egas Moniz, 1649-028 Lisbon, Portugal. diana-reis@fm.ul.pt
Brain research (Netherlands) Jul 5 2005, 1049 (1) p52-60, ISSN 0006-8993--Print Journal Code: 0045503
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
We previously described that vasoactive intestinal peptide (VIP) increases synaptic transmission to hippocampal CA1 pyramidal cells at concentrations known to activate VIP-selective receptors (%VPAC1% and VPAC2) but not the PACAP-selective PAC1 receptor. We now investigated the involvement of %VPAC1% and VPAC2 receptors in the effects elicited by VIP as well as the transduction pathways activated by VIP to cause enhancement

of synaptic transmission. Blockade of either %VPAC1% or VPAC2 receptors with PG 97-269 (100 nM) or PG 99-465 (100 nM) inhibited VIP-induced enhancement of synaptic transmission. Selective activation of %VPAC1% receptors with [K15, R16, L27] VIP(1-7)/GRF(8-27) (10 nM) or of VPAC2 receptors with RO 25-1553 (10 nM) increased synaptic transmission to CA1 pyramidal cells, and this increase was larger when both agonists were applied together. Inhibition of either PKA with H-89 (1 microM) or PKC with GF109203X (1 microM) attenuated the effect of VIP (1 nM). GF109203X (1 microM) abolished the effect of the %VPAC1% agonist [K15, R16, L27] VIP(1-7)/GRF(8-27) (10 nM) on hippocampal synaptic transmission but that effect was not changed by H-89 (1 microM). The effect of RO 25-1553 (100 nM) obtained in the presence of both the PAC1 and %VPAC1% %antagonists%, M65 (30 nM) and PG 97-269 (100 nM), was strongly inhibited by H-89 (1 microM) but not GF109203X (1 microM). It is concluded that VIP enhances synaptic transmission to CA1 pyramidal cell dendrites through %VPAC1% and VPAC2 receptor activation. %VPAC1%-mediated actions are dependent on PKC activity, and VPAC2-mediated actions are responsible for the PKA-dependent actions of VIP on CA1 hippocampal transmission.
Record Date Created: 20050620
Record Date Completed: 20051115

2/7/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

15446342 PMID: 15870879
Expression of vasoactive intestinal peptide and functional VIP receptors in human prostate cancer: %antagonistic% action of a growth-hormone-releasing hormone analog.
Collado Beatriz; Carmena Maria J; Sanchez-Chapado Manuel; Ruiz-Villaespesa Antonio; Bajo Ana M; Fernandez-Martinez Ana B; Varga Jozsef L; Schally Andrew V; Prieto Juan C
Department of Biochemistry and Molecular Biology, University of Alcala, Spain.
International journal of oncology (Greece) Jun 2005, 26 (6) p1629-35 , ISSN 1019-6439--Print Journal Code: 9306042
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Vasoactive intestinal peptide (VIP) functions as a mitogenic agent in the human prostate gland acting by autocrine/paracrine mechanisms. Here we extend knowledge on the VIP system (expression of VIP and VIP receptors, functionality of VIP receptors) at this level by analyzing the differences between human normal prostate and prostate carcinoma specimens. RT-PCR showed the expression of mRNA for VIP in normal and malignant tissues, whereas VIP levels, as measured by enzyme immuno-analysis, were about two times higher in adenocarcinoma samples. Real-time RT-PCR indicated a minor expression of VPAC2 receptors in the prostate gland, as well as the overexpression of %VPAC1% and PAC1 receptors in malignant tissue specimens. Radio-labeled binding experiments with [125I]VIP showed an increased number of VIP binding sites (2.5 times for the high- and 1.7 times for the low-affinity sites) during malignant transformation, whereas the affinity values were unaffected. The receptors were functional in control and cancer tissues as shown by the ability of increasing VIP doses to stimulate adenylate cyclase activity. Interestingly, JV-1-53 (a GHRH-related peptide analog) (at 0.1 microM) behaved as a potent VIP %antagonist% since it inhibited by 60% the maximal VIP effect upon the enzyme activity. The results further explain the mechanisms of the autocrine/paracrine actions of VIP in human prostate and prostatic carcinoma through the observation of differences between healthy tissue and malignant transformation. Moreover, present data support the potential usefulness of VIP and/or synthetic peptide analogs for diagnostic or radiotherapeutic purposes as well as for long-term peptide therapy in this malignancy.
Record Date Created: 20050504
Record Date Completed: 20050726

2/7/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

15438702 PMID: 15661828
Analysis of the role of the PAC1 receptor in neutrophil recruitment, acute-phase response, and nitric oxide production in septic shock.
Martinez Carmen; Juarranz Yasmina; Abad Catalina; Arranz Alicia; Miguel Begona G; Rosignoli Florencia; Leceta Javier; Gomariz Rosa P
Department of Cell Biology, Faculty of Medicine, Complutense University, Madrid, Spain. cmmora@bio.ucm.es
Journal of leukocyte biology (United States) May 2005, 77 (5) p729-38, ISSN 0741-5400--Print Journal Code: 8405628
Publishing Model Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Infections caused by Gram-negative bacteria constitute one of the major causes of septic shock, which results from the inability of the immune system to limit bacterial spread during the ongoing infection. In the last decade, it has been demonstrated that vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) are two endogenous immunopeptides, which together with three G protein-coupled receptors (%VPAC1% , VPAC2, and PAC1) exert a significant, therapeutic effect attenuating the deleterious consequences of septic shock by balancing pro- and anti-inflammatory factors. We have recently shown PAC1 receptor involvement in vivo as an anti-inflammatory receptor, at least in part, by attenuating lipopolysaccharide-induced production of proinflammatory interleukin-6. The present study deepens in the protective role of PAC1 receptor in septic shock, elucidating its involvement in the modulation of neutrophil recruitment and in the expression of different molecular sensors such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1, fibrinogen, serum amyloid A, and nitric oxide as important, systemic players of the development of septic shock. Our results, using a mice deficient in PAC1 and a PAC1 %antagonist%, show that VIP and PACAP as well as the PAC1 receptor are involved in neutrophil recruitment in different target organs, in adhesion molecules expression, and in coagulation-related molecule fibrinogen synthesis. Thus, this study provides some important insights with respect to the involvement of PAC1 into the complexities of sepsis and represents an advantage for the design of more specific drugs complementing standard intensive care therapy in severe sepsis, confirming VIP and PACAP as candidates for multitarget therapy of septic shock.
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Record Date Completed: 20050712
Date of Electronic Publication: 20050120

2/7/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

15397627 PMID: 15711593
Antisecretory actions of a novel vasoactive intestinal polypeptide (VIP) %antagonist% in human and rat small intestine.
Banks Matthew R; Farthing Michael J G; Robberecht Patrick; Burleigh David E
Department of Adult and Paediatric Gastroenterology, St Bartholomew's and The Royal London School of Medicine and Dentistry, Clinical Research Centre, Newark Street, London E1 2AD.
British journal of pharmacology (England) Apr 2005, 144 (7) p994-1001, ISSN 0007-1188--Print Journal Code: 7502536
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Vasoactive intestinal peptide (VIP) has been demonstrated in intestinal mucosal neurones and elicits chloride secretion from enterocytes. These

findings have led to the proposal that VIP is a secretomotor neurotransmitter. Confirmation of such a role may now be possible with the development of PG 97-269, a high-affinity, selective %antagonist% of VIP type 1 (%VPAC1%) receptor, which is expressed by gut epithelial cells. We have evaluated the VIP antagonism and antisecretory potential of this novel compound using in vitro and in vivo models of intestinal secretion. Monolayers of the human colonic cell line (T84) and muscle-stripped preparations of rat jejunum and human ileum were set up in Ussing chambers for recording of transepithelial resistance and short-circuit current. Ussing chambers were modified to allow electrical stimulation of mucosal neurones. Effects of PG 97-269 on enterotoxin-induced secretion were investigated in perfused rat jejunum in vivo. PG 97-269 competitively antagonised VIP in T84 monolayers. In rat jejunum and human ileum, responses to VIP were inhibited as were responses of rat jejunum to electrical stimulation of mucosal neurons. In perfused rat jejunum, PG 97-269 abolished the effects of VIP on fluid and electrolyte transport and attenuated cholera toxin and Escherichia coli heat labile toxin-induced net fluid and electrolyte secretion. PG 97-269 is a competitive %antagonist% of enterocyte VIP receptors and effectively inhibits responses of rat and human intestinal mucosa to VIP. Antagonism of secretory responses to electrical stimulation of mucosal neurons and lumenal application of enterotoxins imply a secretory role for VIP in these processes.
Record Date Created: 20050404
Record Date Completed: 20050929

2/7/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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15294508 PMID: 15514088
VPAC2-R mediates the lipolytic effects of pituitary adenylate cyclase-activating polypeptide/vasoactive intestinal polypeptide in primary rat adipocytes.
Akesson Lina; Ahren Bo; Edgren Gudrun; Degerman Eva
Section for Molecular Signaling, Department of Cell and Molecular Biology, Biomedical Center C11, Lund University, SE-221 84 Lund, Sweden. lina@akesson@.nu
Endocrinology (United States) Feb 2005, 146 (2) p744-50, ISSN 0013-7227--Print Journal Code: 0375040
Publishing Model Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The neuropeptides pituitary adenylate cyclase-activating polypeptide (PACAP) and vasoactive intestinal polypeptide (VIP) are structurally and functionally related. Their actions have been shown to be mediated by three different receptor subtypes: PAC1-R, which has exclusive affinity for PACAP, and %VPAC1%-R and VPAC2-R, which have equal affinity for PACAP and VIP. We recently showed that PACAP38 induces lipolysis in rat adipocytes, and in the present study we examined whether VIP has similar effects and which of the three receptors mediates this PACAP/VIP action. We showed by RT-PCR that all three receptor subtypes are present in rat adipocytes. We demonstrated that VIP (1-100 nm), like PACAP38, stimulates lipolysis in isolated adipocytes, as determined by glycerol release. By a pharmacological approach, using %antagonists% and agonists specific for the receptor subtypes, we elucidated the mechanisms by which PACAP38 and VIP mediate their lipolytic effects. We found that %antagonists% of PAC1-R [PACAP(6-38)] and %VPAC1%-R (PG97-269) did not affect lipolysis induced by 0.1-100 nm PACAP38 or VIP, and that a %VPAC1% -R agonist [K15, R16, L27VIP(1-7)GRF(8-27)] did not affect lipolysis at 1-1000 nm. However, two different VPAC2-R agonists [Hexa-VIP(1-28) and Ro25-1553] clearly mimicked the lipolytic effect of PACAP38 and VIP. In addition, the VPAC2-R %antagonist% PG99-465 (100 nm) caused right-shifted dose-response curves of PACAP38- and VIP-induced lipolysis. These results therefore provide evidence that all three PACAP/VIP receptor subtypes are expressed in primary rat adipocytes, but that the VPAC2-R subtype is responsible for mediating the lipolytic effects induced by PACAP38 and VIP.
Record Date Created: 20050114
Record Date Completed: 20050217
Date of Electronic Publication: 20041028

2/7/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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15255532 PMID: 15589042
Human H9 cells proliferation is differently controlled by vasoactive intestinal peptide or peptide histidine methionine: implication of a GTP-insensitive form of %VPAC1% receptor.
Goursaud Stephanie; Pineau Nicolas; Becq-Giraudon Laetitia; Gressens Pierre; Muller Jean-Marc; Janet Thierry
IPBC CNRS-UMR 6187 Pole Biologie Sante, 40 avenue du Recteur Pineau, 86022 Poitiers, France.
Journal of neuroimmunology (Netherlands) Jan 2005, 158 (1-2) p94-105 , ISSN 0165-5728--Print Journal Code: 8109498
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The proliferation of human lymphoblastoma cell line (H9) was differently stimulated by Peptide Histidine Methionine (PHM) and Vasoactive Intestinal Peptide (VIP). PHM induced a cyclic AMP (cAMP) accumulation, abolished by Adenylate Cyclase (AC) inhibitors leading to a loss of proliferative effect. VIP mitogenic activity was Pertussis toxin (PTX) sensitive and AC inhibitors insensitive. Pharmacological experiments performed on H9 membranes with or without a GTP analogue indicated expression of both GTP-insensitive and -sensitive PHM/VIP high-affinity binding sites (HA). H9 cells expressed only the %VPAC1% receptor. VIP(10-28), known as a %VPAC1% %antagonist% , bond to all GTP-insensitive PHM sites and inhibited evenly the PHM and VIP mitogenic actions. These data strongly suggested different mechanisms initiated by VIP and PHM and highlighted the key role of GTP-insensitive binding sites in the control of cell proliferation.
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Record Date Completed: 20050307

2/7/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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15138727 PMID: 15501526
Ac His1 [D-Phe2, K15, R16, L27] VIP (3-7)/GRF (8-27)--a %VPAC1% receptor %antagonist%--is an inverse agonist on two constitutively active truncated %VPAC1% receptors.
Vertongen Pascale; Langlet Christelle; Langer Ingrid; Gaspard Nathalie; Robberecht Patrick
Department of Biochemistry and Nutrition, School of Medicine, Universite Libre de Bruxelles, Bat G/E, CP 611, B-1070 Bruxelles, Belgium. pvertong@ulb.ac.be
Peptides (United States) Nov 2004, 25 (11) p1943-9, ISSN 0196-9781 --Print Journal Code: 8008690
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
C-terminally truncated human VPAC(1) receptors were constructed and stably transfected in Chinese hamster ovary (CHO) cells. Selected clones expressing comparable receptor densities were studied for ligand's binding properties, basal and stimulated adenylate cyclase activity. The wild-type (1-457) receptor served as reference. The binding properties of all the constructions were preserved. As judged by the intrinsic activity of the partial agonist Q(3)-VIP, the shortest receptors have a moderate impairment of the coupling efficacy to G(alpha s) protein. Cells expressing the VPAC(1) (1-436) and (1-441) truncated receptors had a two- to three-fold higher basal adenylate cyclase activity than those expressing the wild-type

or the VPAC(1) (1-444), (1-433), (1-429), (1-421) and (1-398) receptor. The stimulatory effect of VIP and other agonist was preserved. This suggested that VPAC(1) (1-436) and (1-441) receptors had a constitutive activity. The selective VPAC(1) receptor %antagonist% Ac His(1) [D-Phe(2), K(15), R(16), L(27)] VIP (3-7)/GRF (8-27) reduced by 60% the basal activity with an EC(50) value of 3 nM comparable to its IC(50) value for binding. This agonist behaved thus like an inverse agonist on the constitutively active VPAC(1) receptors generated by C-terminal truncation and expressed in CHO cells.
Record Date Created: 20041025
Record Date Completed: 20050421

2/7/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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14913934 PMID: 15171718
Vasoactive intestinal peptide (VIP) stimulates cortisol secretion from the H295 human adrenocortical tumour cell line via %VPAC1% receptors.
Nicol M R; Cobb V J; Williams B C; Morley S D; Walker S W; Mason J I
University of Edinburgh, Division of Reproductive and Developmental Sciences (Clinical Biochemistry Section), 49 Little France Crescent, Edinburgh EH16 4SB, Scotland, UK. moira.nicol@ed.ac.uk
Journal of molecular endocrinology (England) Jun 2004, 32 (3) p869-77, ISSN 0952-5041--Print Journal Code: 8902617
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Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Vasoactive intestinal peptide (VIP) shows a wide tissue distribution and exerts numerous physiological actions. VIP was shown in a dose-dependent manner to increase cortisol secretion in the NCI-H295R human adrenocortical carcinoma (H295) cell line (threshold dose 3.3x10(-10) M, maximal dose 10(-7) M), coupled with a parallel increase in cAMP accumulation. Receptor-specific agonists were employed to determine which of the two known VIP receptor subtypes was involved in cortisol secretion. Treatment with the %VPAC1% receptor agonist, [K(15), R(16), L(27)]VIP(1-7)/GRF(8-27), produced a dose-dependent increase in H295 cell cortisol secretion (threshold dose 10(-11) M, maximal dose 10(-7) M) similar to that seen with VIP. Meanwhile, the high-affinity VPAC2 receptor agonist, RO-25-1553, failed to stimulate significantly cortisol or cAMP production from H295 cells. Inhibition of VIP-mediated H295 cell cortisol secretion by PG97-269, a competitive %VPAC1%-specific %antagonist%, produced parallel shifts of the dose-response curve and a Schild regression slope of 0.99, indicating competitive inhibition at a single receptor subtype. VIP is known also to interact with the PAC1 receptor, albeit with lower affinity (EC(50) of approximately 200 nM) than the homologous ligand, PACAP (EC(50) of approximately 0.5 nM). PACAP stimulated cortisol secretion from H295 cells (EC(50) of 0.3 nM), suggesting the presence of functional PAC1 receptors. However, stimulation of cortisol secretion by nanomolar concentrations of VIP (EC(50) of 5 nM), coupled with real-time PCR estimation that %VPAC1% receptor transcripts appear 1000-fold more abundant than PAC1 transcripts in H295 cells, makes it unlikely that VIP signals via PAC1 receptors. Together, these data suggest that VIP directly stimulates cortisol secretion from H295 cells via activation of the %VPAC1% receptor subtype.
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Record Date Completed: 20050524

2/7/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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14857800 PMID: 15109935
Multiple signal pathways coupling VIP and PACAP receptors to calcium channels in hamster submandibular ganglion neurons.
Kamaishi Hideaki; Endoh Takayuki; Suzuki Takashi
Department of Physiology, Tokyo Dental College, 1-2-2, Masago, Mihama, Chiba 261-8502, Japan.
Autonomic neuroscience - basic & clinical (Netherlands) Mar 31 2004, 111 (1) p15-26, ISSN 1566-0702--Print Journal Code: 100909359
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The Vasoactive intestinal polypeptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) are two novel neuropeptides which produce particular biological effects caused by interaction with G-protein-coupled receptors. We have shown in a previous study where VIP and PACAP 38 inhibit voltage-dependent calcium channel (VDCC) currents (ICa) via G-proteins in hamster submandibular ganglion (SMG) neurons. In this study, we attempt to further characterize the signal transduction pathways of VIP-and PACAP 38-induced modulation of ICa. Application of 1 microM VIP and PACAP 38 inhibited ICa by 33.0 +/- 3.1% and 36.8 +/- 2.6%, respectively (mean +/- S.E.M., n = 8). Application of strong voltage prepulse attenuated PACAP 38-induced inhibition of ICa. Pretreatment of cAMP dependent protein kinase (PKA) activator attenuated VIP-induced inhibition, but not the PACAP 38-induced inhibition. Intracellular dialysis of the PKA inhibitor attenuated the VIP-induced inhibition; but not the PACAP 38-induced inhibition. Pretreatment of protein kinase C (PKC) activator and inhibitor attenuated VIP-induced inhibition, but not the PACAP 38-induced inhibition. Pretreatment of cholera toxin (CTX) attenuated PACAP 38-induced inhibition of ICa. These findings indicate that there are multiple signaling pathways in VIP and PACAP 38-induced inhibitions of ICa: one pathway would be the %VPAC1% /VPAC2 receptors-induced inhibition involving both the PKA and PKC, and another one concerns the PAC1 receptor-induced inhibition via Gs-protein betagamma subunits. The VIP-and PACAP 38-induced facilitation of ICa can be observed in the SMG neurons in addition to inhibiting of ICa. Copyright 2004 Elsevier B.V.
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Record Date Completed: 20040708

2/7/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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14825125 PMID: 15067323
The pituitary adenylate cyclase-activating polypeptide is a physiological inhibitor of platelet activation.
Freson Kathleen; Hashimoto Hitoshi; Thys Chantal; Wittevrongel Christine; Danloy Sophie; Morita Yoshiko; Shintani Norihito; Tomiyama Yoshiaki; Vermylen Jos; Hoylaerts Marc F; Baba Akemichi; Van Geet Chris
Center for Molecular and Vascular Biology, University Hospital Gasthuisberg, University of Leuven, Leuven, Belgium. kathleen.freson@med.kuleuven.ac.be
Journal of clinical investigation (United States) Mar 2004, 113 (6) p905-12, ISSN 0021-9738--Print Journal Code: 7802877
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The pituitary adenylate cyclase-activating polypeptide (PACAP) is a neuropeptide of the vasoactive intestinal peptide/secretin/glucagon superfamily. Studies in two related patients with a partial trisomy 18p revealed three copies of the PACAP gene and elevated PACAP concentrations in plasma. The patients suffer from severe mental retardation and have a bleeding tendency with mild thrombocytopenia, and their fibroblasts show increased PACAP mRNA levels. The PACAP receptor (vasoactive intestinal peptide/pituitary adenylate cyclase-activating peptide receptor 1 [%VPAC1%]) in platelets and fibroblasts is coupled to adenylyl cyclase activation. Accordingly, we found increased basal cAMP levels in patients' platelets and fibroblasts, providing a basis for the reduced platelet aggregation in these patients. Megakaryocyte-specific transgenic overexpression of PACAP in mice correspondingly increased PACAP release from platelets, reduced platelet activation, and prolonged the tail bleeding time. In contrast, the

PACAP %antagonist% PACAP(6-38) or a monoclonal PACAP antibody enhanced the collagen-induced aggregation of normal human platelets, and in PACAP knockout mice, an increased platelet sensitivity toward collagen was found. Thus, we found that PACAP modulates platelet function and demonstrated what we believe to be the first hemostatic defect associated with PACAP overexpression; our study suggests the therapeutic potential to manage arterial thrombosis or bleeding by administration of PACAP mimetics or inhibitors, respectively.
Record Date Created: 20040406
Record Date Completed: 20040503

2/7/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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14776625 PMID: 15003357
Helospectin I and II evoke vasodilation in the intact peripheral microcirculation.
Tsueshita Takaya; Onyukusel Hayat; Sethi Varun; Gandhi Salil; Rubinstein Israel
Department of Medicine (M/C 719), University of Illinois at Chicago, 840 South Wood Street, Room 173, Chicago, IL 60612-7323, USA.
Peptides (United States) Jan 2004, 25 (1) p65-9, ISSN 0196-9781--Print Journal Code: 8008690
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Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Helospectin I and II, two closely related mammalian neuropeptides of the secretin/glucagons/vasoactive intestinal peptide (VIP) superfamily of peptides, are co-localized with VIP in nerve fibers surrounding vascular smooth muscle. However, the role if any, VIP receptors play in transducing the vasorelaxant effects of helospectin I and II in the intact peripheral microcirculation is uncertain. The purpose of this study was to determine whether helospectin I and II elicit vasodilation in the intact peripheral microcirculation and, if so, whether this response is mediated, in part, by VIP or pituitary adenylate cyclase activating peptide (PACAP) receptor engagement, and through local elaboration of cyclooxygenase products of arachidonic acid metabolism. Using intravital microscopy, we found that suffusion of helospectin I and II (each, 1.0 nmol) evoked potent vasodilation and of similar magnitude in the intact hamster cheek pouch microcirculation ($P < 0.05$). Suffusion of 0.1 nmol helospectin I and II had no significant effects on arteriolar diameter. Pretreatment with VIP(10-28), a %VPAC1%/VPAC2 receptor %antagonist% , or PACAP(6-38), a PAC1/VPAC2 receptor %antagonist%, had no significant effects on helospectin I- and II-induced responses. In addition, pretreatment with indomethacin had no significant effects on helospectin I- and II-induced vasodilation. Collectively, these data indicate that helospectin I and II evoke potent vasodilation in the intact peripheral microcirculation that is not transduced by VIP or PACAP receptors nor through cyclooxygenase products of arachidonic acid metabolism.
Record Date Created: 20040308
Record Date Completed: 20041222

2/7/24 (Item 24 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2007 Dialog. All rts. reserv.

14724738 PMID: 14578481
Evidence for the involvement of %VPAC1% and VPAC2 receptors in pressure-induced vasodilatation in rodents.
Fizanne Lionel; Sigaudo-Roussel Dominique; Saumet Jean Louis; Fromy Berengere
Laboratory of Physiology, University of Angers, Angers, France.
Journal of physiology (England) Jan 15 2004, 554 (Pt 2) p519-28, ISSN 0022-3751--Print Journal Code: 0266262
Publishing Model Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
A transient increase in skin blood flow in response to an innocuous local pressure application, defined as pressure-induced vasodilatation (PIV), delays the occurrence of ischaemia, suggesting a protective feature against applied pressure. The PIV response depends on capsaicin-sensitive nerve fibres and calcitonin gene-related peptide (CGRP) has been shown to be involved. In these fibres, CGRP coexists with pituitary adenylate cyclase-activating polypeptide (PACAP). Three distinct receptors mediate the biological effects of PACAP: %VPAC1% and VPAC2 receptors binding with the same affinity for PACAP and vasoactive intestinal peptide and PAC1 receptors showing high selectivity for PACAP. Because the receptors are widely expressed in the nervous system and in the skin, we hypothesized that at least one of them is involved in PIV development. To verify this hypothesis, we used [D-p-Cl-Phe(6),Leu(17)]-VIP (nonspecific %antagonist% of %VPAC1%/VPAC2 receptors), PG 97-269 (%antagonist% of %VPAC1% receptors), PACAP(6-38) (%antagonist% of VPAC2/PAC1 receptors) and Max.d.4 (%antagonist% of PAC1 receptors) in anaesthetized rodents. The blockade of %VPAC1%/VPAC2, %VPAC1% or VPAC2/PAC1 receptors eliminated the PIV response, whereas PAC1 blockade had no effect, demonstrating an involvement of %VPAC1% /VPAC2 receptors in PIV development. Moreover, endothelium-independent and -dependent vasodilator responses were unchanged by the %VPAC1%/VPAC2 %antagonist% . Thus, the absence of a PIV response following %VPAC1%/VPAC2 blockade cannot be explained by any dysfunction of the vascular smooth muscle or endothelial vasodilator capacity. The involvement of %VPAC1%/VPAC2 receptors in the development of PIV seems to imply a series relationship in which each receptor type (CGRP, %VPAC1%, VPAC2) is necessary for the full transmission of the response.
Record Date Created: 20040126
Record Date Completed: 20040916
Date of Electronic Publication: 20031024

2/7/25 (Item 25 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2007 Dialog. All rts. reserv.

14696136 PMID: 14706566
VIP receptor %antagonists% inhibit mammary carcinogenesis in C3(1)SV40T antigen mice.
Moody Terry W; Dudek James; Zakowicz Halina; Walters James; Jensen Robert T; Petricoin Emmanual; Couldrey Chris; Green Jeff E
Department of Health and Human Services, National Institutes of Health, NCI Office of the Director, Center for Cancer Research, NCI, Bethesda, MD 20892, USA. moodyt@mail.nih.gov
Life sciences (England) Jan 30 2004, 74 (11) p1345-57, ISSN 0024-3205--Print Journal Code: 0375521
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The effects of a vasoactive intestinal peptide (VIP) receptor %antagonist% on mammary carcinogenesis were investigated using the C3(1)SV40T antigen (ag) mice. Ten microg/day VIPhybrid (VIPhyb) administered daily subcutaneously increased significantly the survival of C3(1)SV40Tag mice. At 5.2 months, VIPhyb significantly reduced the mammary tumor burden in C3(1)SV40Tag mice relative to control animals. 125I-VIP bound with high affinity to mouse mammary tumor homogenate. Because (Lys15, Arg16, Leu27)VIP1-7GRF8-27 (%VPAC1% selective) but not Ro25-1553 (VPAC2 selective) inhibited specific 125I-VIP binding to mammary tumor membranes with high affinity, %VPAC1% receptors predominate. By RT-PCR, %VPAC1% receptor mRNA was detected in mammary tumors. By Western blot, a major 60 Kdalton band was detected in mammary tumor extracts using %VPAC1% receptor antisera. By immunocytochemistry, %VPAC1%-R immunostaining was detected in the cytosol and plasma membrane but not the nucleus of fixed mammary tumor tissue. Using laser capture microdissected tumor cells and surface enhanced laser desorption/ionization (SELDI) techniques on mammary tumor cells, the

proteomic profile was altered in mice treated with VIPhyb. Because %VPAC1% receptor %antagonists% increase the survival and reduce the tumor burden in C3(1)SV40Tag mice, they may function as chemopreventive agents in mammary cancer.
Record Date Created: 20040106
Record Date Completed: 20040218

2/7/26 (Item 26 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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14405731 PMID: 12750439
A lymphocyte-generated fragment of vasoactive intestinal peptide with %VPAC1% agonist activity and VPAC2 %antagonist% effects.
Summers Monica A; O'Dorisio M Sue; Cox Mary O; Lara-Marquez Maria; Goetzl Edward J
Depaertment of Pediatrics, University of Iowa City, Iowa City, Iowa 52242, USA.
Journal of pharmacology and experimental therapeutics (United States) Aug 2003, 306 (2) p638-45, ISSN 0022-3565--Print Journal Code: 0376362
Contract/Grant No.: R01 CA41997; CA; NCI; R01 CA90236; CA; NCI
Publishing Model Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Vasoactive intestinal peptide receptors 1 (%VPAC1%) and 2 (VPAC2) have been identified in humans. Cell lines expressing only %VPAC1% (HT-29) or VPAC2 (Molt-4b) were identified using real-time reverse transcriptase polymerase chain reaction. Vasoactive intestinal peptide (VIP) and related peptides, VIP-6-28, VIP4-28, and VIP10-28, previously isolated from cultures of human leukocytes, were evaluated for their ability to bind to %VPAC1% and VPAC2 and to increase the levels of cAMP in HT-29 and Molt-4b cells. VIP bound to membranes of HT-29 colon carcinoma cells and Molt-4b lymphoblasts with high affinity (KD = 1.6 +/- 0.2 and 1.7 +/- 0.9 nM, respectively). VIP4-28 also demonstrated high-affinity binding (KD = 1.7 +/- 0.2 and 1.7 +/- 0.7 nM in HT-29 and Molt-4b, respectively). VIP and VIP4-28 are potent %VPAC1% agonists, inducing maximal 200- and 400-fold increases in cAMP, respectively. VIP demonstrated weak VPAC2 agonist activity, inducing a maximal 14-fold increase in cAMP. VIP4-28 had no VPAC2 agonist activity but demonstrated potent VPAC2 %antagonist% activity. VIP4-28 inhibited VPAC2-mediated increases in cAMP in Molt-4b cells up to 95%, but had no %antagonistic% effect on %VPAC1%. Lymphoblasts did not hydrolyze VIP4-28 to a form with %VPAC1% %antagonist% activity. VIP4-28 thus is a lymphocyte-generated VIP fragment with potent agonist activity for %VPAC1% and potent %antagonist% activity for VPAC2.
Record Date Created: 20030721
Record Date Completed: 20030828
Date of Electronic Publication: 20030515

2/7/27 (Item 27 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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14405557 PMID: 12754213
Inhibition of interferon (IFN) gamma-induced Jak-STAT1 activation in microglia by vasoactive intestinal peptide: inhibitory effect on CD40, IFN-induced protein-10, and inducible nitric-oxide synthase expression.
Delgado Mario
Instituto de Parasitologia y Biomedicina Lopez-Neyra, Consejo Superior de Investigaciones Cientificas, Granada 18001, Spain. mdelgado@ipb.csic.es
Journal of biological chemistry (United States) Jul 25 2003, 278 (30) p27620-9, ISSN 0021-9258--Print Journal Code: 2985121R
Publishing Model Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Interferon (IFN)-gamma is one of the most important microglia stimulators in vivo participating in inflammation and Th1 activation/differentiation. IFN-gamma-mediated signaling involves the activation of the Jak/STAT1 pathway. The neuropeptides vasoactive intestinal peptide (VIP) and the pituitary adenylate cyclase activating polypeptide (PACAP) are two potent microglia-deactivating factors that inhibit the production of proinflammatory mediators in vitro and in vivo. The present study investigated the molecular mechanisms involved in the VIP/PACAP regulation of several IFN-gamma-induced microglia-derived factors, including IFN-gamma-inducible protein-10 (IP-10), inducible nitric-oxide synthase (iNOS), and CD40. The results indicate that VIP/PACAP inhibit Jak1-2 and STAT1 phosphorylation, and the binding of activated STAT1 to the IFN-gamma activated site motif in the IFN regulatory factor-1 and CD40 promoter and to the IFN-stimulated response element motif of the IP-10 promoter. Through its effect in the IFN-gamma-induced Jak/STAT1 pathway, VIP and PACAP are able to control the gene expression of IP-10, CD40, and iNOS, three microglia-derived mediators that play an essential role in several pathologies, i.e. inflammation and autoimmune disorders. The effects of VIP/PACAP are mediated through the specific receptor %VPAC1% and the cAMP/protein kinase A transduction pathway. Because IFN-gamma is a major stimulator of innate and adaptive immune responses in vivo, the down-regulation of IFN-gamma-induced gene expression by VIP and PACAP could represent a significant element in the regulation of the inflammatory response in the central nervous system by endogenous neuropeptides.
Record Date Created: 20030721
Record Date Completed: 20030826
Date of Electronic Publication: 20030515

2/7/28 (Item 28 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2007 Dialog. All rts. reserv.

14380393 PMID: 12839880
VIP and PACAP are autocrine factors that protect the androgen-independent prostate cancer cell line PC-3 from apoptosis induced by serum withdrawal.
Gutierrez-Canas Irene; Rodriguez-Henche Nieves; Bolanos Oscar; Carmena Maria J; Prieto Juan C; Juarranz Maria G
Department of Biochemistry and Molecular Biology, University of Alcala, E-28871 Alcala de Henares, Spain.
British journal of pharmacology (England) Jul 2003, 139 (5) p1050-8, ISSN 0007-1188--Print Journal Code: 7502536
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
1. In the present study, we describe the expression of the neuropeptides vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) as well as their receptors in PC-3 cells, a human prostate cancer cell line. In addition, we have investigated their role in apoptosis induced by serum starvation. 2. By RT-PCR and immunocytochemistry assays, we have demonstrated the production of VIP and PACAP in PC-3 cells. 3. We have demonstrated by RT-PCR and binding assays the expression of common PACAP/VIP (VPAC(1) and VPAC(2)) receptors, but not PACAP-specific (PAC(1)) receptors. The pharmacological profile of [(125)I]-VIP binding assays was as follows: VPAC(1) %antagonist%=VPAC(1) agonist>VIP>VPAC(2) agonist (IC(50)=1.2, 1.5, 2.3 and 30 nM, respectively). In addition, both receptor subtypes are functional since VIP, PACAP-27 or VPAC(1) and VPAC(2) agonists all increased the intracellular levels of cAMP. 4. The expression of both peptides and their receptors is similar in serum-cultured and serum-deprived PC-3 cells. The treatment of serum-deprived PC-3 cells with exogenous VIP or PACAP-27 increases cell number and viability in a dose-dependent manner, as demonstrated by cellular counting and MTT assays. The increased cell survival is exerted through the VPAC(1) receptor, since a VPAC(1), but not VPAC(2), receptor agonist, mimics the effects and a VPAC(1) receptor %antagonist% blocks it. Moreover, VIP and PACAP-27 inhibit genomic DNA fragmentation in PC-3 cells triggered by serum starvation, and increase the immunoreactivity of the

antiapoptotic protein bcl-2. 5. Our results suggest that VIP and PACAP are autocrine/paracrine factors that protect PC-3 cells from apoptosis through %VPAC1% receptors.
Record Date Created: 20030703
Record Date Completed: 20040309

2/7/29 (Item 29 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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14186787 PMID: 12598410
Inhibition of intestinal dipeptide transport by the neuropeptide VIP is an anti-absorptive effect via the %VPAC1% receptor in a human enterocyte-like cell line (Caco-2).
Anderson Catriona M H; Mendoza Maria E; Kennedy David J; Raldua Demetrio; Thwaites David T
School of Cell & Molecular Biosciences, The Medical School, University of Newcastle upon Tyne, Newcastle upon Tyne NE2 4HH.
British journal of pharmacology (England) Feb 2003, 138 (4) p564-73, ISSN 0007-1188--Print Journal Code: 7502536
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
1. Optimal dipeptide and peptidomimetic drug transport across the intestinal mucosal surface is dependent upon the co-operative functional activity of the di/tripeptide transporter hPepT1 and the Na(+)/H(+) exchanger NHE3. The ability of the anti-absorptive enteric neuropeptide VIP (vasoactive intestinal peptide) to modulate dipeptide uptake was determined using human intestinal (Caco-2) epithelial cell monolayers. 2. Uptake of glycylsarcosine (Gly-Sar) across the apical membrane of Caco-2 cell monolayers is inhibited by basolateral exposure to either VIP, pituitary adenylate cyclase-activating polypeptide (PACAP), or the VPAC(1) receptor agonist [(11,22,28)Ala]-VIP. Inhibition of Gly-Sar uptake is observed only in the presence of extracellular Na(+). Reverse-transcription polymerase chain reaction (RT-PCR) demonstrates that VPAC(1) mRNA is expressed in Caco-2 cells whereas VPAC(2) mRNA is not detected. 3. The VIP-induced inhibition of Gly-Sar uptake is abolished in the presence of the protein kinase A (PKA) inhibitor H-89 (N-[2-(p-bromocinnamylamino)ethyl]-5-isoquino linesulfonamide.2HCl). 4. (22)Na(+) uptake across the apical membrane is inhibited by the selective NHE3 inhibitor S1611. Experiments with BCECF [2',7'-bis(2-carboxyethyl)-5(6)-carboxyfluorescein]-loaded Caco-2 cells demonstrate that VIP reduces the NHE3-dependent recovery of intracellular pH (pH(i)) after dipeptide-induced acidification. Western blot of Caco-2 cell protein demonstrates expression of the NHE regulatory factor NHERF1 (expression of which is thought to be required for PKA-mediated inhibition of NHE3). 5. VIP has no effect on Gly-Sar uptake in the presence of S1611 suggesting that VIP and S1611 both modulate dipeptide uptake via the same mechanism. 6. These observations demonstrate that VIP (and PACAP) modulate activity of the H(+)/dipeptide transporter hPepT1 in a Na(+)-dependent manner consistent with the modulation being indirect through inhibition of NHE3.
Record Date Created: 20030224
Record Date Completed: 20030827

2/7/30 (Item 30 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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14162828 PMID: 12559130
Lysine 195 and aspartate 196 in the first extracellular loop of the %VPAC1% receptor are essential for high affinity binding of agonists but not of %antagonists%.
Langer I; Vertongen P; Perret J; Waelbroeck M; Robberecht P
Department of Biological Chemistry and Nutrition, Faculty of Medicine, Universite Libre de Bruxelles. Bat GE, CP 611, 808 Route de Lennik, B-1070 Brussels, Belgium. ilanger@ulb.ac.be
Neuropharmacology (England) Jan 2003, 44 (1) p125-31, ISSN 0028-3908--Print Journal Code: 0236217
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The role in ligand recognition and receptor activation of two adjacent charged residues (lysine 195 and aspartate 196) in the first extracellular loop of the human VPAC(1) receptor was investigated in stably transfected CHO cells expressing the wild type or point mutated receptors.Replacement of lysine 195 by glutamine or of aspartate 196 by asparagine reduced the agonists' ability to stimulate adenylate cyclase activity; VIP behaved like a partial agonist and a partial agonist behaved as an %antagonist%. The receptor's capacity to recognize agonists was reduced but %antagonists%' affinity was unaffected. Both results suggesting that the two charged residues are essential for VPAC(1) receptor activation. On the other hand, the double mutant was less severely affected than single mutants suggesting that hydrogen bonds may partially compensate the loss of charged residues. But the inversion of the residues affected receptor recognition and activation more markedly suggesting that the two charged residues do not interact directly.
Record Date Created: 20030131
Record Date Completed: 20030430

2/7/31 (Item 31 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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14081971 PMID: 12529932
VPAC receptors for VIP and PACAP.
Laburthe M; Couvineau A; Marie J C
Neuroendocrinology and Cell Biology, INSERM U410, Faculte de Medecine, Xavier Bichat, 75018 Paris, France. laburthe@bichat.inserm.fr
Receptors & channels (England) 2002, 8 (3-4) p137-53, ISSN 1060-6823--Print Journal Code: 9315376
Publishing Model Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
VIP and PACAP are two prominent neuropeptides that share two common G protein-coupled receptors, %VPAC1% and VPAC2, while PACAP has an additional specific receptor, PAC1. This article reviews the present knowledge regarding various aspects of VPAC receptors including: 1) receptor specificity toward natural VIP-related peptides and pharmacology of synthetic agonists or %antagonists% ; 2) genomic organization and chromosomal localization; 3) signaling and established or putative interactions with G proteins or accessory proteins such as RAMPs or PDZ-containing proteins; 4) molecular basis of ligand-receptor interaction as determined by site-directed mutagenesis, construction of receptor chimeras, and structural modeling; 5) constitutively active receptor mutants; 6) short-term (desensitization, internalization, phosphorylation) and long-term (transcription) regulations and transgenic models; 7) receptor polymorphisms. (158 Refs.)
Record Date Created: 20030117
Record Date Completed: 20030514

2/7/32 (Item 32 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2007 Dialog. All rts. reserv.

14073463 PMID: 12510388
[Physiological significance of pituitary adenylate cyclase-activating polypeptide (PACAP) in the nervous system]
Hashimoto Hitoshi
Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565-0871, Japan. hasimoto@phs.osaka-u.ac.jp

Yakugaku zasshi. Journal of the Pharmaceutical Society of Japan (Japan) Dec 2002, 122 (12) p1109-21, ISSN 0031-6903--Print Journal Code: 0413613
Publishing Model Print
Document type: Journal Article; Review ; English Abstract
Languages: JAPANESE
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Pituitary adenylate cyclase-activating polypeptide (PACAP) has been conserved remarkably during evolution and is widely expressed in the nervous system across phyla. PACAP has an amino acid sequence homology of 68% with that of vasoactive intestinal polypeptide (VIP) and of 37% with that of secretin, indicating that PACAP is a member of the VIP/glucagon/secretin superfamily. PACAP exerts its actions via three heptahelical G-protein-linked receptors: one PACAP-specific (PAC1) receptor and two receptors (%VPAC1% and VPAC2) shared with VIP. PACAP stimulates several different signaling cascades in neurons, leading to the activation of adenylate cyclase, phospholipase C, and mitogen-activated protein kinase and mobilization of calcium. Although PACAP and VIP have no apparent homology with calcitonin and parathyroid hormone (PTH), PAC1, VPAC, secretin, glucagon, glucagon-like peptide 1, growth hormone-releasing hormone, calcitonin, and PTH/PTH-related peptide receptors are related to each other and constitute a subfamily of the G-protein-coupled receptors. Distribution analysis of PACAP and its receptors and pharmacological studies have elucidated its pleiotropic effects in the central and peripheral nervous systems. However, the relevance of the pharmacological PACAP effects to the actual physiological activities of endogenous PACAP has not been addressed, because potent and selective low-molecular-weight PACAP %antagonists% have not yet been developed. To assess the function of PACAP in vivo, we have recently generated PAC1 receptor- and PACAP-targeted mice, and provided evidence that PACAP plays a previously uncharacterized role in the regulation of psychomotor behaviors. In this review, we focus on the physiological and or pathophysiological roles mediated by PACAP in the nervous system. (39 Refs.)
Record Date Created: 20030103
Record Date Completed: 20030312

2/7/33 (Item 33 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

14033104 PMID: 12453189
Maxadilan activates PAC1 receptors expressed in Xenopus laevis xelanophores.
Pereira Phyllis; Reddy Vermuri B; Kounga Kounga; Bello Ysabel; Lerner Ethan
Department of Dermatology, Cutaneous Biology Research Center, Massachusetts General Hospital/Harvard Medical School, Charlestown, MA 02129, USA.
Pigment cell research / sponsored by the European Society for Pigment Cell Research and the International Pigment Cell Society (Denmark) Dec 2002, 15 (6) p461-6, ISSN 0893-5785--Print Journal Code: 8800247
Contract/Grant No.: R01 AR42005; AR; NIAMS
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Functional interactions between ligands and their cognate receptors can be investigated using the ability of melanophores from Xenopus laevis to disperse or aggregate their pigment granules in response to alterations in the intracellular levels of second messengers. We have examined the response of long-term lines of cultured melanophores from X. laevis to pituitary adenylate cyclase activating peptide (PACAP), a neuropeptide with vasodilatory activity, and maxadilan, a vasodilatory peptide present in the salivary gland extracts of the blood feeding sand fly. Pituitary adenylate cyclase activating peptide increased the intracellular levels of cyclic adenosine monophosphate (cAMP) and induced pigment dispersion in the pigment cells, confirming that melanophores express an endogenous PACAP receptor. Maxadilan did not induce a response in non-transfected melanophores. When the melanophores were transfected with complementary DNA (cDNA) from the three different members of the PACAP receptor family, maxadilan induced pigment dispersion specifically and cAMP accumulation in melanophores transfected with the cDNA for PAC1 receptors but not %VPAC1% or VPAC2 receptors. A melanophore line was generated that stably expresses the PAC1 receptor.
Record Date Created: 20021127
Record Date Completed: 20030513

2/7/34 (Item 34 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13920241 PMID: 12225791
Vasoactive intestinal peptide (VIP) inhibits the proliferation of bone marrow progenitors through the %VPAC1% receptor.
Rameshwar Pranela; Gascon Pedro; Oh Hyun S; Denny Thomas N; Zhu Goafa; Ganea Doina
Department of Medicine, UMDNJ-New Jersey Medical School, Newark, NJ 07103, USA. rameshwa@umdnj.edu
Experimental hematology (Netherlands) Sep 2002, 30 (9) p1001-9, ISSN 0301-472X--Print Journal Code: 0402313
Contract/Grant No.: CA-89868; CA; NCI; HL-54973; HL; NHLBI; HL-57675; HL; NHLBI
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
OBJECTIVE: The cellular and molecular mechanisms of hematopoietic stimulation have been studied. However, an understanding of negative effects in the hematopoietic system remains elusive. To this end, we studied the effects of vasoactive intestinal peptide (VIP) on bone marrow (BM) progenitors. MATERIALS AND METHODS: Different BM cell subsets were used to perform clonogenic assay for granulocytic (CFU-GM) or erythroid (BFU-E and CFU-E) progenitors with 10(-7)-10(-13) M VIP. The relevant receptor was verified with specific %antagonists% , or agonists, semi-quantitative RT-PCR, and chemical cross-linking studies with stromal membranes. RESULTS: Assays performed with unfractionated mononuclear cells and enriched CD34(+) cells showed dose-dependent inhibition on BM progenitors with significant inhibition up to 10(-10) M. Nylon wool separated cells, which depleted stroma, reversed the inhibitory effects of VIP between 10 and 20%. Combined experimental evaluation indicated that the effects of VIP on BM functions are mediated through the type 1 receptor (%VPAC1%). VIP induced the production of TGF-beta and TNF-alpha in BM mononuclear cells and stroma. These cytokines are partly involved in reversing the suppressive effects of VIP on CFU-GM. CONCLUSIONS: The effect of VIP on BM progenitors could be mediated through direct and indirect mechanism. Direct effects were evident by the suppressive effects of VIP on clonogenic assays with highly purified CD34(+) cells. Indirect effects were mediated through putative functions of the stromal cells and the production of TGF-beta and TNF-alpha.
Record Date Created: 20020912
Record Date Completed: 20021108

2/7/35 (Item 35 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13917257 PMID: 12220741
Molecular pharmacology and structure of VPAC Receptors for VIP and PACAP.
Laburthe M; Couvineau A
Neuroendocrinology and Cell Biology, INSERM U410, Faculte de Medecine Xavier Bichat, 75018, Paris, France. laburthe@bichat.inserm.fr
Regulatory peptides (Netherlands) Oct 15 2002, 108 (2-3) p165-73, ISSN 0167-0115--Print Journal Code: 8100479
Publishing Model Print

Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
VIP and PACAP are two prominent neuropeptides which share two common G protein-coupled receptors %VPAC1% and VPAC2 while PACAP has an additional specific receptor PAC1. This paper reviews the present knowledge regarding three aspects of VPAC receptors including: (i). receptor specificity towards natural VIP-related peptides and pharmacology of synthetic agonists or %antagonists% ; (ii). receptor signaling; (iii). molecular basis of ligand-receptor interaction as determined by site-directed mutagenesis, construction of receptor chimeras and structural modeling. (91 Refs.)
Record Date Created: 20020910
Record Date Completed: 20030410

2/7/36 (Item 36 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2007 Dialog. All rts. reserv.

13861772 PMID: 12151535
Pituitary adenylate cyclase-activating polypeptide and vasoactive intestinal peptide inhibit dendritic growth in cultured sympathetic neurons.
Drahushuk Karen; Connell Terry D; Higgins Dennis
Department of Pharmacology and Toxicology and the Witebsky Center for Microbial Pathogenesis and Immunology, State University of New York at Buffalo, Buffalo, New York 14214, USA. drahushu@buffalo.edu
Journal of neuroscience - the official journal of the Society for Neuroscience (United States) Aug 1 2002, 22 (15) p6560-9, ISSN 1529-2401--Electronic Journal Code: 8102140
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Pituitary adenylate cyclase-activating polypeptide (PACAP) and vasoactive intestinal peptide (VIP) are related neuropeptides that are released by the preganglionic sympathetic axons. These peptides have previously been implicated in the regulation of sympathetic neurotransmitter metabolism and cell survival in postganglionic sympathetic neurons. In this study we consider the possibility that PACAP and VIP also affect the morphological development of these neurons. Postganglionic rat sympathetic neurons formed extensive dendritic arbors after exposure to bone morphogenetic protein-7 (BMP-7) in vitro. PACAP and VIP reduced BMP-7-induced dendritic growth by approximately 70-90%, and this suppression was maintained for 3 weeks. However, neither PACAP nor VIP affected axonal growth or cell survival. The actions of PACAP and VIP appear to be mediated by PAC1 receptors because their effects were suppressed by an %antagonist% that binds to PAC1 and VPAC2 receptors (PACAP6-38), but not by an %antagonist% that binds to the %VPAC1% and VPAC2 receptors. Moreover, exposure to PACAP and VIP caused phosphorylation and nuclear translocation of cAMP response element-binding protein, and agents that increase the intracellular concentration of cAMP mimicked the PACAP-induced inhibition of dendritic growth. These data suggest that peptides released by preganglionic nerves modulate dendritic growth in sympathetic neurons by a cAMP-dependent mechanism.
Record Date Created: 20020801
Record Date Completed: 20020903

2/7/37 (Item 37 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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13828541 PMID: 12112366
Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit chemokine production in activated microglia.
Delgado Mario; Jonakait G Miller; Ganea Doina
Department of Biological Sciences, Rutgers University, Newark, New Jersey 07102, USA.
Glia (United States) Aug 2002, 39 (2) p148-61, ISSN 0894-1491--Print Journal Code: 8806785
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Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Microglia react to even minor disturbances in CNS homeostasis and function as critical regulators of CNS inflammation. Activated microglia secrete inflammatory mediators such as cytokines and chemokines, which contribute to the pathophysiological changes associated with several neuroimmunologic disorders. Microglia-derived inflammatory chemokines recruit various populations of immune cells, which initiate and maintain the inflammatory response against foreign antigens. Entry and retention of activated immune cells in the CNS is a common denominator in a variety of traumatic, ischemic, and degenerative diseases. Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) are two structurally related neuropeptides that function as potent anti-inflammatory factors in the periphery. Here we investigated the effects of VIP and PACAP on chemokine production by activated microglia. VIP and PACAP inhibit the expression of the microglia-derived CXC chemokines MIP-2 and KC, and of the CC chemokines MIP-1alpha, -1beta, MCP-1, and RANTES. The inhibition of chemokine gene expression correlates with an inhibitory effect of VIP/PACAP on NFkB binding. The VIP/PACAP inhibition of both chemokine production and of NFkB binding is mediated through the specific receptor %VPAC1% and involves a cAMP-dependent intracellular pathway. Of biological significance is the fact that the inhibition of chemokine production by VIP/PACAP leads to a significant reduction in the chemotactic activity generated by activated microglia for peripheral leukocytes, i.e., neutrophils, macrophages, and lymphocytes. Because reduction in the number and activation of infiltrating leukocytes represents an important factor in the control of inflammation in the CNS, VIP and/or PACAP released by neurons during an inflammatory response could serve as neuronal survival factors by limiting the inflammatory process. Copyright 2002 Wiley-Liss, Inc.
Record Date Created: 20020711
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2/7/38 (Item 38 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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13812890 PMID: 12090758
Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit LPS-stimulated MIP-1alpha production and mRNA expression.
Pozo David; Guerrero Juan M; Calvo Juan R
Department of Medical Biochemistry and Molecular Biology, The University of Seville School of Medicine, Sevilla, Spain.
Cytokine (United States) Apr 7 2002, 18 (1) p35-42, ISSN 1043-4666 --Print Journal Code: 9005353
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) are neuropeptides with immunomodulatory properties, including the regulation of several proinflammatory mediators. Such mediators, for example chemokines, influence trafficking of inflammatory cells and contribute to shaping the immune response. In the present work, we studied the effect of VIP and PACAP on the CC chemokine macrophage inflammatory protein-1 alpha (MIP-1alpha) production in LPS-stimulated RAW 264.7 macrophage cell line. VIP and PACAP inhibited the production of MIP-1alpha in a dose-dependent manner and over a broad spectrum of LPS concentrations. The use of selective agonists and %antagonists% of VIP/PACAP receptors showed that type 1 VIP receptor (%VPAC1%) is the major receptor involved, but the type

2 VIP receptor (VPAC2) may be also implicated. By using selective PKA and PKC inhibitors and cAMP mimicked agents, we demonstrated a cAMP-dependent signalling pathway for the inhibitory effect of VIP/PACAP on MIP-1alpha production, although a minor non-mediated cAMP pathway was also involved. mRNA expression studies showed a down-regulation of MIP-1alpha gene expression by VIP and PACAP. Taken together, the present work strongly supports an anti-inflammatory role of VIP and PACAP by a new mechanism associated with impairment of a key component of the chemokine network.
Record Date Created: 20020701
Record Date Completed: 20030221

2/7/39 (Item 39 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13781447 PMID: 12054537
Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit the MEKK1/MEK4/JNK signaling pathway in endotoxin-activated microglia.
Delgado Mario
Departamento Biologia Celular, Facultad de Biologia, Universidad Complutense, Madrid 28040, Spain. mariodm@bio.ucm.es
Biochemical and biophysical research communications (United States) May 3 2002, 293 (2) p771-6, ISSN 0006-291X--Print Journal Code: 0372516
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The vasoactive intestinal peptide (VIP) and the pituitary adenylate cyclase-activating polypeptide (PACAP), two immunomodulatory neuropeptides, act as anti-inflammatory factors for activated microglia, by inhibiting the production of proinflammatory factors. In the present study the effects of VIP/PACAP on the MEKK1/MEK4/JNK transduction pathway and on the subsequent changes in Jun family members, a transduction pathway clearly involved in the activation of microglia cells were examined. VIP/PACAP inhibit MEKK1 activity and the subsequent phosphorylations of MEK4, JNK, and c-Jun, which result in a decrease in the AP-1 binding and a marked change in the composition of AP-1 complexes from c-Jun/c-Fos to JunB/c-Fos. Furthermore, VIP stimulates JunB production in LPS-stimulated microglia. Both inhibition of the MEKK1/MEK4/JNK pathway, leading to a reduction in phosphorylated c-Jun, and the stimulation of JunB are mediated through the specific %VPAC1% receptor and cAMP/PKA pathway. The VIP/PACAP interference with the stress-induced SAPK/JNK pathway in activated microglia may represent a significant element in the regulation of inflammatory response in the CNS by endogenous neuropeptides. Copyright 2002 Elsevier Science (USA).
Record Date Created: 20020610
Record Date Completed: 20020712

2/7/40 (Item 40 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13690148 PMID: 11931347
(N-stearyl, norleucine17)VIPhybrid is a broad spectrum vasoactive intestinal peptide receptor %antagonist%.
Moody Terry W; Jensen Robert T; Fridkin Mati; Gozes Illana
National Cancer Institute, Medicine Branch, Rockville, MD 20850, USA. moodyt@bprb.nci.nih.gov
Journal of molecular neuroscience - MN (United States) Feb-Apr 2002, 18 (1-2) p29-35, ISSN 0895-8696--Print Journal Code: 9002991
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The effects of a (N-stearyl, Norleucine17) vasoactive intestinal peptide hybrid ((SN)VIPhybrid) on cells stably transfected with VPAC,, VPAC2, or PAC1 receptors were investigated. (SN)VIPhybrid inhibited specific 125I-VIP binding to membranes derived from CHO cells transfected with VPAC, or VPAC2 receptors with high affinity (IC50 = 30 and 50 nM). (SN)VIPhyb inhibited specific 125I-PACAP-27 binding to membranes derived from NIH/3T3 cells transfected with PAC1 receptors with high affinity (IC50 = 65 nM). PACAP-27 caused cAMP elevation in NIH/3T3 cells transfected with PAC1 receptors and the increase cAMP caused by pituitary adenylated cyclase (PACAP) was inhibited by (SN)VIPhyb. Also, the increase in cAMP caused by VIP using CHO cells transfected with %VPAC1% or VPAC2 receptors was antagonized by (SN)VIPhyb. These results indicate that (SN)VIPhyb is an %antagonist% for %VPAC1%, VPAC2, and PAC1 receptors.
Record Date Created: 20020404
Record Date Completed: 20021108

2/7/41 (Item 41 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13625404 PMID: 11836629
Pituitary adenylate cyclase-activating polypeptide and PACAP receptor expression and function in the rat adrenal gland.
Mazzocchi Giuseppina; Malendowicz Ludwik K; Neri Giuliano; Andreis Paola G; Ziolkowska Agnieszka; Gottardo Lucia; Nowak Krzysztof W; Nussdorfer Gastone G
Department of Human Anatomy and Physiology, Section of Anatomy, University of Padua, I-35121 Padua, Italy.
International journal of molecular medicine (Greece) Mar 2002, 9 (3) p233-43, ISSN 1107-3756--Print Journal Code: 9810955
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Pituitary adenylate cyclase-activating polypeptide (PACAP) is a basic 38-amino acid peptide, which acts through three main G protein-coupled VIP/PACAP receptor subtypes, called PAC1, %VPAC1% and VPAC2. We have investigated the expression and function of PACAP and its receptors in the rat adrenal gland. Reverse transcription (RT)-polymerase chain reaction (PCR) and radioimmune assay (RIA) allowed the detection of PACAP expression as mRNA and protein exclusively in adrenal medulla (AM). RT-PCR and quantitative autoradiography, using [(125)I]PACAP and selective VIP/PACAP receptor ligands, demonstrated the expression of PAC1 only in AM, and %VPAC1% and VPAC2 in both AM and zona glomerulosa (ZG), PACAP receptor expression being absent in zona fasciculata/reticularis (ZF/R). PACAP38 concentration-dependently increased aldosterone secretion from dispersed ZG cells and catecholamine secretion from AM tissue, the maximal effective concentration being 10(-7) M. ZF/R cells did not display any secretory response to PACAP38. Aldosterone response of ZG cells to 10(-7) M PACAP38 was unaffected by the PAC1-%antagonist% (A) PACAP(6-38), and significantly decreased by the %VPAC1% -A [Ac-His(1),D-Phe(2),Lys(15),Arg(16)]VIP(3-7) GRF(8-27)-NH(2). Catecholamine response of AM tissue to PACAP38 was reduced, but not abolished, by both PAC1-A and %VPAC1%-A. The VPAC2 agonist (ago) Ro25-1553 elicited sizeable secretory responses from both ZG cells and AM tissue. PACAP38 (10(-7) M) evoked a marked rise in cyclic-AMP (cAMP) and inositol-1,4,5-triphosphate (IP3) production by ZG cells and AM tissue. cAMP response of ZG cells was lowered by %VPAC1%-A, and that of AM tissue by both PAC1-A and %VPAC1%-A. IP3 response of ZG cells and AM tissue was unaffected by PAC1-A and decreased by %VPAC1%-A. VPAC2-ago did not affect cAMP release, but raised IP3 production by both ZG cells and AM tissue. Aldosterone response of ZG cells and catecholamine response of AM tissue to PACAP38 (10(-7) M) were reduced by the adenylate cyclase (AC) and phospholipase-C (PLC) inhibitors (I) SQ-22536 and U-73122, as well as by the protein kinase (PK)A-I H-89 and PKC-I calphostin-C. Conversely, the secretory responses of both ZG and AM preparations to VPAC2-ago were annulled by PLC-I, lowered by PKC-I, and unaffected by either AC-I or PKA-I. Collectively, our findings allow us to conclude that in the rat adrenals: i) PACAP biosynthesis exclusively occurs in the AM; ii) ZG cells are provided with functional %VPAC1% and VPAC2 receptors, whose activation

by PACAP evokes a moderate aldosterone response; iii) AM cells possess all the subtypes of VIP/PACAP receptors, whose activation by PACAP elicits a marked catecholamine response; and iv) PAC1 receptors are coupled to the AC-dependent cascade, %VPAC1% receptors to both the AC- and PLC-dependent cascades, and VPAC2 receptors exclusively to the PLC-dependent cascade.
Record Date Created: 20020211
Record Date Completed: 20020430

2/7/42 (Item 42 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13623314 PMID: 11834941
%VPAC1% is a cellular neuroendocrine receptor expressed on T cells that actively facilitates productive HIV-1 infection.
Branch Donald R; Valenta Linda J E; Yousefi Shida; Sakac Darinka; Singla Ruchi; Bali Meenakshi; Sahai Beni M; Ma Xue-Zhong
Department of Medicine, Institute of Medical Science, University of Toronto, Ontario, Canada.
AIDS (London, England) (England) Feb 15 2002, 16 (3) p309-19, ISSN 0269-9370--Print Journal Code: 8710219
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
OBJECTIVE: A lack of productive HIV-1 infection of Kit225 compared to Jurkat T cells, despite similar levels of CD4 and HIV-1 chemokine co-receptors, was found to correlate with the expression of vasoactive intestinal peptide/pituitary adenylate cyclase activating polypeptide receptor-1 (%VPAC1%). We therefore examined a role for this seven-transmembrane G protein-coupled neuroendocrine receptor in modulating HIV-1 infection. METHODS: Reverse transcription-PCR was used to show the level of %VPAC1% expression in different T-cell lines. A signal-blocking antibody to %VPAC1% was used to examine its inhibiting effect on HIV-1 infection. Transfection of %VPAC1% cDNA in both sense and anti-sense orientation was used to assess the role of %VPAC1% in HIV-1 infection. HIV-1 infection was monitored by gag p24 ELISA using HIV-1IIIB or by luciferase activity using pseudo envelope-typed HXB2-NL4-3-luciferase. Analysis of HIV-1 gag DNA and 2-LTR circles was utilized to examine a possible mechanism for the effect of %VPAC1%. RESULTS: Using %VPAC1% signal blocking antibody, we showed that up to 80% of productive infection with HIV-1IIIB was inhibited. We also demonstrated that HIV-1 gp120 has sequence similarity to the natural ligand for %VPAC1% and postulate that it can activate this receptor directly. Transfection of %VPAC1% cDNA in the anti-sense orientation resulted in a significant loss, up to 50% of productive infection. In contrast, transfection of cells with %VPAC1% in the sense orientation increased the productive infection by more than 15-fold and caused a profound increase in syncytium formation. Furthermore, stimulation of %VPAC1% on primary cells facilitated in vitro infection with HIV-1 HXB2-NL4-3. Analysis of HIV-1 gag DNA indicated that %VPAC1% does not affect viral entry; however, cells that show negligible expression of %VPAC1% may not be productively infected as indicated by a lack of 2-LTR circle formation. CONCLUSION: We have discovered a cellular receptor, %VPAC1% , that is a novel and potent facilitator of HIV-1 infection and thus, is a potentially important new target for therapeutic intervention.
Record Date Created: 20020208
Record Date Completed: 20020520

2/7/43 (Item 43 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13485275 PMID: 11730988
PACAP mediates the neural proliferative pathway of Mastomys enterochromaffin-like cell transformation.
Lauffer J M; Tang L H; Zhang T; Hinoue T; Rahbar S; Odo M; Modlin I M; Kidd M
Surgical Gastric Pathobiology Research Group, Yale University School of Medicine, and West Haven Veterans Administration Medical Center, New Haven, CT 06520-8062, USA.
Regulatory peptides (Netherlands) Dec 15 2001, 102 (2-3) p157-64, ISSN 0167-0115--Print Journal Code: 8100479
Contract/Grant No.: DK-48820; DK; NIDDK
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
BACKGROUND AND AIM: Pituitary adenylate-cyclase activating peptide (PACAP) is a more potent proliferative agent than gastrin for rat enterochromaffin-like (ECL) cell proliferation in vitro. The role of this neurotransmitter during gastrin-mediated ECL cell tumor formation and gastrin-autonomous ECL cell neoplasia is unknown. METHODS AND RESULTS: ECL cell transformation was induced in the Mastomys using 16 wk H2 receptor blockade of acid inhibition. Examination of the epithelial fundic mucosa demonstrated that PACAP-immunoreactivity significantly increased in the tumor mucosa compared to the naive stomach, and was associated with ECL cells. Naive and tumor ECL cells were then purified (approximately 95%) from Mastomys and the presence of all three PACAP/VPAC receptor subtypes was demonstrated by polymerase chain-reaction amplification. Thereafter, cells were maintained in short-term (48 h) primary cultures. PACAP significantly ($p<0.05$) increased 24 h bromo-deoxyuridine uptake (approximately 4-fold) in both cell types with estimated EC(50) values of approximately 4x10(-16) M and approximately 2x10(-16) M, respectively. Specific receptor %antagonists% (PAC1/%VPAC1%) of PACAP competitively inhibited these proliferative effects in naive cells. Oligonucleotide antisense directed against PAC1 significantly inhibited PACAP-stimulated DNA synthesis by approximately 85% ($p<0.05$) in tumor cells. CONCLUSION: PACAP is a potent and effective modulator of ECL cell proliferation. The expression of this neuropeptide and its receptors, particularly PAC1, suggest the existence of a neural regulatory pathway of ECL cell proliferation and transformation.
Record Date Created: 20011203
Record Date Completed: 20020307

2/7/44 (Item 44 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13482203 PMID: 11728828
Neuroendocrine differentiation of the LNCaP prostate cancer cell line maintains the expression and function of VIP and PACAP receptors.
Juarranz M G; Bolanos O; Gutierrez-Canas I; Lerner E A; Robberecht P; Carmena M J; Prieto J C; Rodriguez-Henche N
Department of Biochemistry and Molecular Biology, Universidad de Alcala, 28871, Alcala de Henares, Spain.
Cellular signalling (England) Dec 2001, 13 (12) p887-94, ISSN 0898-6568--Print Journal Code: 8904683
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The molecular mechanisms involved in differentiation of prostate cancer cells to a neuroendocrine (NE) cell phenotype are not well understood. Here we used the androgen-dependent human prostate cancer cell line LNCaP to perform a systematic and broad analysis of the expression, pharmacology, and functionality of vasoactive intestinal peptide (VIP)/pituitary adenylate cyclase-activating peptide (PACAP) receptors. Reverse transcription polymerase chain reaction experiments, together with pharmacological approaches with a set of specific agonists and %antagonists% , demonstrated the presence of the three VIP/PACAP receptor subtypes (PAC1, %VPAC1%, and VPAC2 with a major role for %VPAC1%, acting through adenylate cyclase (AC) stimulation. An essentially similar pattern was observed by NE differentiated cells (4 days after serum deprivation) in spite of the important morphological changes observed. However, the

expression of the prostate-specific antigen (PSA) decreased in NE cells (and increased again by dihydrotestosterone, DHT, treatment). The present demonstration of the induction of NE transdifferentiation in LNCaP cells by increasing concentrations of VIP adds value to previous observations on the role of cAMP in this process, an interesting topic in the comprehension of the molecular changes that are involved in the progression of prostate cancer to androgen independence.
Record Date Created: 20011130
Record Date Completed: 20020110

2/7/45 (Item 45 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13353428 PMID: 11514016
Proline residue 280 in the second extracellular loop (EC2) of the VPAC2 receptor is essential for the receptor structure.
Vertongen P; Solano R M; Juarranz M G; Perret J; Waelbroeck M; Robberecht P
Department of Biochemistry and Nutrition, School of Medicine, Universite Libre de Bruxelles, Bat G/E, CP 611, 808 route de Lennik, B-1070, Bruxelles, Belgium.
Peptides (United States) Sep 2001, 22 (9) p1363-70, ISSN 0196-9781 --Print Journal Code: 8008690
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Inspection of the amino acid sequence of the human %VPAC1% and the VPAC2 receptors after alignment of the conserved residues indicates that the second extracellular loop (EC2) is one amino acid shorter in the %VPAC1% receptor due to the lack of a proline residue in position 294. We hypothesized that this could be of importance for receptor structure and/or for ligand recognition. Insertion by directed mutagenesis of a proline in that position (<Pro>294 %VPAC1%) had little consequence on the binding of several agonists but reduced the affinity for the %VPAC1% %antagonist%. Coupling of the <Pro>294 %VPAC1% receptor to adenylate cyclase was improved, as demonstrated by an increased affinity for VIP and other agonists, and by a shift of the %VPAC1% %antagonist% to partial agonist behavior. Deletion of the proline 280 (DeltaPro280 VPAC2) in the VPAC2 receptor markedly reduced the apparent affinity for all the agonists tested. Replacement of the proline by a glycine residue had a smaller effect on the ligands affinities. The proline residue in the VPAC2 receptor EC2 is thus essential for the receptor structure, and the EC2 domain is involved in ligand recognition and receptor functionality.
Record Date Created: 20010821
Record Date Completed: 20011221

2/7/46 (Item 46 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13289491 PMID: 11441105
Inhibition of endotoxin-induced macrophage chemokine production by vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide in vitro and in vivo.
Delgado M; Ganea D
Department of Biological Sciences, Rutgers University, 101 Warren Street, Newark, NJ 07102, USA.
Journal of immunology (Baltimore, Md. - 1950) (United States) Jul 15 2001, 167 (2) p966-75, ISSN 0022-1767--Print Journal Code: 2985117R
Contract/Grant No.: AI 41786-03; AI; NIAID
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Inflammatory chemokines recruit various populations of immune cells that initiate and maintain the inflammatory response against foreign Ags. Although such a response is necessary for the elimination of the Ag, the inflammation has to be eventually resolved in a healthy organism. Neuropeptides such as vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP), released after antigenic stimulation, contribute to the termination of an inflammatory response primarily by inhibiting the production of proinflammatory cytokines. Here we investigated the effects of VIP and PACAP on chemokine production. We report that VIP and PACAP inhibit the expression of the macrophage-derived CXC chemokines macrophage inflammatory protein-2 and KC (IL-8), and of the CC chemokines MIP-1alpha, MIP-1beta, monocyte chemoattractant protein 1, and RANTES in vivo and in vitro. The inhibition of chemokine gene expression correlates with an inhibitory effect of VIP/PACAP on NF-kappaB binding and transactivating activity. The VIP/PACAP inhibition of both chemokine production and of NF-kappaB binding and transactivating activity is mediated through the specific VIP receptor %VPAC1%, and involves both cAMP-dependent and -independent intracellular pathways. In an in vivo model of acute peritonitis, the inhibition of chemokine production by VIP/PACAP leads to a significant reduction in the recruitment of polymorphonuclear cells, macrophages, and lymphocytes into the peritoneal cavity. These findings support the proposed role of VIP and PACAP as key endogenous anti-inflammatory agents and describe a novel mechanism, i.e., the inhibition of the production of macrophage-derived chemokines.
Record Date Created: 20010706
Record Date Completed: 20011004

2/7/47 (Item 47 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13119016 PMID: 11013258
Two basic residues of the h-%VPAC1% receptor second transmembrane helix are essential for ligand binding and signal transduction.
Solano R M; Langer I; Perret J; Vertongen P; Juarranz M G; Robberecht P; Waelbroeck M
Laboratoire de Chimie Biologique et de la Nutrition, Faculte de Medecine, Universite Libre de Bruxelles, 808 route de Lennik, Building G/E, CP 611, B-1070 Brussels, Belgium.
Journal of biological chemistry (United States) Jan 12 2001, 276 (2) p1084-8, ISSN 0021-9258--Print Journal Code: 2985121R
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
We mutated the vasoactive intestinal peptide (VIP) Asp(3) residue and two VPAC(1) receptor second transmembrane helix basic residues (Arg(188) and Lys(195)). VIP had a lower affinity for R188Q, R188L, K195Q, and K195I VPAC(1) receptors than for VPAC(1) receptors. [Asn(3)] VIP and [Gln(3)] VIP had lower affinities than VIP for VPAC(1) receptors but higher affinities for the mutant receptors; the two basic amino acids facilitated the introduction of the negatively charged aspartate inside the transmembrane domain. The resulting interaction was necessary for receptor activation. 1/[Asn(3)] VIP and [Gln(3)] VIP were partial agonists at VPAC(1) receptors; 2/VIP did not fully activate the K195Q, K195I, R188Q, and R188L VPAC(1) receptors; a VIP analogue ([Arg(16)] VIP) was more efficient than VIP at the four mutated receptors; and [Asn(3)] VIP and [Gln(3)] VIP were more efficient than VIP at the R188Q and R188L VPAC(1) receptors; 3/the [Asp(3)] negative charge did not contribute to the recognition of the VIP(1) %antagonist% , [AcHis(1),D-Phe(2),Lys(15),Arg(16),Leu(27)] VIP ()/growth hormone releasing factor (8-27). This is the first demonstration that, to activate the VPAC(1) receptor, the Asp(3) side chain of VIP must penetrate within the transmembrane domain, in close proximity to two highly conserved basic amino acids from transmembrane 2.
Record Date Created: 20010306
Record Date Completed: 20010405

2/7/48 (Item 48 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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13063109 PMID: 11029467
Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit nuclear factor-kappa B-dependent gene activation at multiple levels in the human monocytic cell line THP-1.
Delgado M; Ganea D
Department of Biological Sciences, Rutgers University, Newark, New Jersey 07102, USA.
Journal of biological chemistry (UNITED STATES) Jan 5 2001, 276 (1) p369-80, ISSN 0021-9258--Print Journal Code: 2985121R
Contract/Grant No.: AI 041786-03; AI; NIAID
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The neuropeptides vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) suppress monocyte/macrophage production of proinflammatory agents. The transcription factor NF-kappa B regulates the transcription of most agents. VIP/PACAP inhibit NF-kappa B transactivation in the lipopolysaccharide-stimulated human monocytic cell line THP-1 at multiple levels. First, VIP/PACAP inhibit p65 nuclear translocation and NF-kappa B DNA binding by stabilizing the inhibitor I kappa B alpha. Second, VIP/PACAP induce phosphorylation of the CRE-binding protein (CREB) and its binding to the CREB-binding protein (CBP). This results in a decrease in p65.CBP complexes, which further reduces NF-kappa B transactivation. Third, VIP and PACAP reduce the phosphorylation of the TATA box-binding protein (TBP), resulting in a reduction in TBP binding to both p65 and the TATA box. All these effects are mediated through the specific receptor %VPAC1%. The cAMP/cAMP-dependent protein kinase pathway mediates the effects on CBP and TBP, whereas a cAMP-independent pathway is the major transducer for the effects on p65 nuclear translocation. Since NF-kappaB represents a focal point for various stimuli and induces the expression of many proinflammatory genes, its targeting by VIP and PACAP positions them as important anti-inflammatory agents. The VIP/PACAP inhibition of NF-kappa B at various levels and through different transduction pathways could offer a significant advantage over other anti-inflammatory agents.
Record Date Created: 20010208
Record Date Completed: 20010208

2/7/49 (Item 49 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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13000126 PMID: 11193832
%VPAC1% receptors and lung cancer.
Moody T W; Walters J; Casibang M; Zia F; Gozes Y
National Cancer Institute, Medicine Branch, Cell and Cancer Biology Department, Rockville, Maryland 20850, USA. moodyt@bprb.nci.nih.gov
Annals of the New York Academy of Sciences (United States) 2000, 921 p26-32, ISSN 0077-8923--Print Journal Code: 7506858
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
VIP/PACAP are autocrine growth factors for lung cancer. VIP and/or PACAP mRNA is present in most lung cancer cell lines examined. Although mRNA for VPAC2-R is not common, %VPAC1%-R and PAC1-R mRNA is present in many lung cancer cell lines. 125I-VIP binds with high affinity to lung cancer cells and specific 125I-VIP binding is inhibited with high affinity by (Lys15, Arg16, Leu27)VIP1-7 GRF8-27, the %VPAC1%-R specific agonist, but not by Ro25-1553(18), the VPAC2-R specific agonist. VIP elevates cAMP and increases c-fos gene expression. The increase in cAMP and c-fos mRNA caused by VIP is inhibited by SN(VH). (SH)VH inhibited the proliferation of NCIH1299 cells in the MTT assay, which is based on cytotoxicity. In a recent cell line screen, (SN)VH inhibited the growth of 51 of 56 cancer cell lines including leukemia, lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, breast cancer, and prostate cancer (T. Moody, unpublished). It remains to be determined if (SN)VH will be useful for treatment of a wide variety of cancers.
Record Date Created: 20010117
Record Date Completed: 20010201

2/7/50 (Item 50 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2007 Dialog. All rts. reserv.

13000125 PMID: 11193811
In vitro evaluation of VIP/PACAP receptors in healthy and diseased human tissues. Clinical implications.
Reubi J C
Division of Cell Biology and Experimental Cancer Research, Institute of Pathology, University of Berne, P.O. Box 62, Murtenstrasse 31, CH-3010 Berne, Switzerland. reubi@patho.unibe.ch
Annals of the New York Academy of Sciences (United States) 2000, 921 p1-25, ISSN 0077-8923--Print Journal Code: 7506858
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The evaluation of peptide receptors in man is relevant to identifying the physiological target tissues of a given peptide and to selecting diseases with a sufficient receptor overexpression for diagnostic or therapeutic intervention. VIP/PACAP receptors have been evaluated in normal and diseased human non-neuronal tissues by using in vitro receptor autoradiography with 125I-VIP or 125I-PACAP in tissue sections. As assessed by subtype-selective VIP analogs, VIP receptors of the %VPAC1% subtype are found in a wide variety of tissues including liver, breast, kidney, prostate, ureter, bladder, pancreatic ducts, gastrointestinal mucosa, lung, thyroid, adipose, and lymphoid tissues. VPAC2 receptors are predominantly found in vessels and smooth muscles, whereas PAC1 receptors are present in the adrenal medulla. VIP/PACAP receptors are expressed in the majority of the most frequently occurring human tumors, including breast, prostate, pancreas, lung, colon, stomach, liver, and bladder carcinomas, as well as lymphomas and meningiomas, predominantly as %VPAC1% receptors, as do their tissues of origin. Although leiomyomas predominantly express VPAC2 receptors, glial tumors, pituitary adenomas, neuroblastomas, paragangliomas, pheochromocytomas, and endometrial carcinomas preferentially express PAC1 receptors. The very wide distribution of VIP/PACAP receptors in the normal human body is indicative of the key role of these peptides in human physiology and pathophysiology. Moreover, the receptor expression in tumors is the molecular basis for clinical applications of VIP/PACAP such as in vivo scintigraphy and radiotherapy of tumors as well as VIP/PACAP analog treatment for tumor growth inhibition.
Record Date Created: 20010117
Record Date Completed: 20010201

2/7/51 (Item 51 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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12988545 PMID: 11138925
VIP and PACAP 38 modulate ibotenate-induced neuronal heterotopias in the newborn hamster neocortex.
Gressens P; Arquie C; Hill J M; Marret S; Sahir N; Robberecht P; Evrard P
INSERM E 9935, H pital Robert-Debre, Paris, France.
Journal of neuropathology and experimental neurology (United States) Dec 2000, 59 (12) p1051-62, ISSN 0022-3069--Print Journal Code: 2985192R
Publishing Model Print
Document type: Journal Article

Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Intracerebral administration of ibotenate produces, through activation of N-methyl-D-aspartate (NMDA) receptors, neuronal heterotopias in the newborn hamster neocortex: high doses of ibotenate induce periventricular and subcortical neuronal heterotopias, while low doses of ibotenate produce intracortical heterotopias and molecular layer ectopias. Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) are closely related peptides with neurotrophic properties. They share common %VPAC1% and VPAC2 receptors, which use cAMP as a second messenger. Previous studies have shown that VIP prevents excitotoxic neuronal death and exacerbates glutamate-induced c-fos neuronal expression. In order to gain new insight into the molecular control of neuronal migration, the present study examined the effects of VIP and PACAP on ibotenate-induced heterotopias in the newborn hamster. Co-treatment with VIP and a high dose of ibotenate produced a pattern of neuronal heterotopias similar to the one observed in animals treated with low doses of ibotenate alone. Pups co-injected with a low dose of ibotenate and a VIP %antagonist% displayed cortical dysgeneses similar to those observed in animals treated with high doses of ibotenate alone. The modulating effects of VIP on excitotoxin-induced heterotopias were mimicked by forskolin, PACAP, and by a specific VPAC2 receptor agonist but not by a %VPAC1% agonist, and were blocked by a protein kinase A (PKA) inhibitor. Taken together, these data suggest that VIP and PACAP can attenuate ibotenate-induced heterotopias in newborn hamster and that this effect is mediated by the VPAC2 receptor utilizing the cAMP-PKA pathway.
Record Date Created: 20010102
Record Date Completed: 20010111

2/7/52 (Item 52 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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12948777 PMID: 11093139
Anti-inflammatory properties of the type 1 and type 2 vasoactive intestinal peptide receptors: role in lethal endotoxic shock.
Delgado M; Gomariz R P; Martinez C; Abad C; Leceta J
Departamento de Biologia Celular, Facultad de Biologia, Universidad Complutense, Madrid, Spain.
European journal of immunology (GERMANY) Nov 2000, 30 (11) p3236-46, ISSN 0014-2980--Print Journal Code: 1273201
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Vasoactive intestinal peptide (VIP) is a neuropeptide that can modulate several immune aspects. Previous reports showed that VIP attenuates the deleterious consequences of septic shock by inhibiting the production of pro-inflammatory agents and stimulating the production of anti-inflammatory cytokines in activated macrophages. In this study, by using selective VIP agonists, we investigated the differential involvement of the VIP receptors in the anti-inflammatory role of VIP. Both the type 1 VIP receptor (%VPAC1%) agonist, [K(15), R(16), L(27)] VIP 1-7-GRF 8-27, and the type 2 VIP receptor (VPAC2) agonist, Ro25-1553, protected mice from lethal endotoxemia by inhibiting the macrophage-derived pro-inflammatory mediators IL-6, TNF-alpha, IL-12 and NO, and by stimulating the production of the anti-inflammatory cytokine IL-10. In addition, both VIP and %VPAC1% agonist, but not the VPAC2 agonist, reduced in vitro and in vivo the expression of the co-stimulatory B7. 1/B7.2 molecules, and the subsequent stimulatory activity for T helper cells in stimulated macrophages. The higher effectiveness of the %VPAC1% agonist compared with the VPAC2 agonist suggests that %VPAC1% is the major mediator of the anti-inflammatory action of VIP. Since VIP and the two agonists appear to affect multiple cytokines and inflammatory factors, they might provide a more efficient therapeutical alternative to the use of specific cytokine antibodies or %antagonists%.
Record Date Created: 20010104
Record Date Completed: 20010104

2/7/53 (Item 53 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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12829022 PMID: 10947803
VIP and PACAP potentiation of nicotinic ACh-evoked currents in rat parasympathetic neurons is mediated by G-protein activation.
Liu D M; Cuevas J; Adams D J
Department of Physiology and Pharmacology, University of Queensland, Brisbane, Australia.
European journal of neuroscience (FRANCE) Jul 2000, 12 (7) p2243-51, ISSN 0953-816X--Print Journal Code: 8918110
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The effects of vasoactive intestinal polypeptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP27 and PACAP38) on isolated parasympathetic neurons of rat intracardiac and submandibular ganglia were examined under voltage clamp using whole-cell patch-clamp recording techniques. VIP and PACAP (</= 10 nM) selectively and reversibly increased the affinity of nicotinic acetylcholine receptor channels (nAChRs) for their agonists resulting in a potentiation of acetylcholine (ACh)-evoked whole-cell currents at low agonist concentrations. VIP-induced potentiation was observed with either ACh or nicotine as the cholinergic agonist. The VIP- but not the PACAP-induced potentiation of ACh-evoked currents was inhibited by [Ac-Tyr1, D-Phe2]-GRF 1-29, amide (100 nM), a selective %antagonist% of %VPAC1% and VPAC2 receptors; whereas the PACAP38- but not the VIP-induced potentiation was inhibited by 100 nM PACAP6-38, a PAC1 and VPAC2 receptor %antagonist%. The signal transduction pathway mediating VIP- and PACAP-induced potentiation of nicotinic ACh-evoked currents involves a pertussis toxin (PTX)-sensitive G-protein. Intracellular application of 200 microM GTPgammaS or GDPbetaS inhibited VIP-induced potentiation of ACh-evoked whole-cell currents. GTPgammaS alone potentiated ACh- and nicotine-evoked currents and the magnitude of these currents was not further increased by VIP or PACAP. The G-protein subtype modulating the neuronal nAChRs was examined by intracellular dialysis with antibodies directed against alphao, alphai-1,2, alphai-3 or beta G-protein subunits. Only the anti-Galphao and anti-Gbeta antibodies significantly inhibited the effect of VIP and PACAP on ACh-evoked currents. The potentiation of ACh-evoked currents by VIP and PACAP may be mediated by a membrane-delimited signal transduction cascade involving the PTX-sensitive Go protein.
Record Date Created: 20000919
Record Date Completed: 20000919

2/7/54 (Item 54 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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12817985 PMID: 10933794
Inhibition of expression of the type I G protein-coupled receptor for vasoactive intestinal peptide (%VPAC1%) by hammerhead ribozymes.
Jabrane-Ferrat N; Pollock A S; Goetzl E J
Departments of Medicine and Microbiology-Immunology and Department of Medicine, Veterans Affairs Medical Center, University of California, San Francisco, California 94143-0711, USA.
Biochemistry (UNITED STATES) Aug 15 2000, 39 (32) p9771-7, ISSN 0006-2960--Print Journal Code: 0370623
Contract/Grant No.: AI 29912; AI; NIAID; DK 31398; DK; NIDDK
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Vasoactive intestinal peptide (VIP) is a neuromediator expressed widely

in the nervous, gastrointestinal, respiratory, and immune systems. Two G protein-coupled receptors (GPCRs), designated %VPAC1% and VPAC2, bind VIP with high affinity and transduce increases in [cyclic AMP](i) and [Ca(2+)](i). As there are no potent %VPAC1%- or VPAC2-selective %antagonists% , a hammerhead ribozyme (Rz) strategy capable of in vivo application was adopted to inactivate individual domains of %VPAC1%. Three Rzs were designed to cleave mRNA encoding the amino terminus, the third intracellular loop, and the cytoplasmic tail of human %VPAC1% and were introduced by transfection into HEK-293 cells expressing recombinant human %VPAC1%. Each Rz specifically degraded %VPAC1% mRNA and down-regulated %VPAC1% protein and VIP-binding activity, as assessed by ribonuclease protection assays, Western blots, and binding of (125)I-VIP. Rz-mediated down-regulation of %VPAC1% was associated with up to 75% suppression of VIP signaling of increases in [cyclic AMP](i) and [IP3](i), and of cyclic AMP response element-luciferase reports. The Rz specific for the amino terminus inhibited %VPAC1% expression and signaling to the greatest extent. VIP-evoked cellular responses thus appear to be proportional to the level of %VPAC1% expression. Specific Rzs may be powerful tools for manipulating tissue-specific contributions of GPCRs in vitro and in vivo.
Record Date Created: 20000905
Record Date Completed: 20000905

2/7/55 (Item 55 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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12754218 PMID: 10861043
Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit T cell-mediated cytotoxicity by inhibiting Fas ligand expression.
Delgado M; Ganea D
Department of Biological Sciences, Rutgers University, Newark, NJ 07102, USA.
Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Jul 1 2000, 165 (1) p114-23, ISSN 0022-1767--Print Journal Code: 2985117R
Contract/Grant No.: AI041786-02; AI; NIAID
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
We reported recently that the neuropeptides vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) protect CD4+ T cells against Ag-induced apoptosis by down-regulating the expression of Fas ligand (FasL). Because the cytotoxic activity of CD8+ CTLs is mediated through two mechanisms, which involve the perforin/granzyme and the FasL/Fas pathways, in this study we investigated the effects of VIP/PACAP on the generation and activity of allogeneic CTLs, of CD8+ T1 and T2 effector cells and of alloreactive peritoneal exudate cytotoxic T cells (PEL) generated in vivo. VIP/PACAP did not affect perforin/granzyme-mediated cytotoxicity, perforin gene expression, or granzyme B enzymatic activity, but drastically inhibited FasL/Fas-mediated cytotoxicity against allogeneic or syngeneic Fas-bearing targets. VIP/PACAP inhibit CTL generation, but not the activity of competent CTLs. The inhibition is associated with a profound down-regulation of FasL expression, and these effects are mediated through both %VPAC1% and VPAC2 receptors. VIP/PACAP inhibit the FasL/Fas-mediated cytotoxicity of T1 effectors and do not affect T2 cytotoxicity, which is entirely perforin/granzyme mediated. Similar effects were observed in vivo. Both the FasL/Fas-mediated cytotoxicity and FasL expression of cytotoxic allogeneic PELs generated in vivo in the presence of VIP or PACAP were significantly reduced. We conclude that, similar to their effect on CD4+ T cells, the two structurally related neuropeptides inhibit FasL expression in CD8+ cytotoxic T cells and the subsequent lysis of Fas-bearing target cells.
Record Date Created: 20000731
Record Date Completed: 20000731

2/7/56 (Item 56 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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12713349 PMID: 10808055
Vasoactive intestinal peptide (VIP) inhibits TGF-beta1 production in murine macrophages.
Sun W; Tadmori I; Yang L; Delgado M; Ganea D
Department of Biological Sciences, Rutgers University, 101 Warren St., Newark, NJ 07102, USA.
Journal of neuroimmunology (NETHERLANDS) Jul 10 2000, 107 (1) p88-99 , ISSN 0165-5728--Print Journal Code: 8109498
Contract/Grant No.: AI041786-02; AI; NIAID
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Vasoactive intestinal peptide (VIP) and the structurally related neuropeptide pituitary adenylate cyclase-activating polypeptide (PACAP), produced and/or released in the lymphoid microenvironment act primarily as macrophage- and T cell-deactivating agents. In the present study we investigate the effect of VIP and PACAP on the production of TGF-beta1 in the macrophage cell line Raw 264.7 and in peritoneal macrophages. The two neuropeptides do not affect the baseline TGF-beta1 production by unstimulated macrophages, but reduce dramatically TGF-beta1 production by LPS-stimulated macrophages. The effects are mediated through the specific receptors %VPAC1%, VPAC2, and PAC1. The effect of VIP is mediated primarily through the cAMP pathway, whereas PACAP activates both the cAMP and the protein kinase C pathway. VIP reduces the TGF-beta1 steady-state mRNA levels in both peritoneal macrophages and Raw 264.7 cells treated with LPS. A similar effect is observed upon the in vivo administration of VIP. This report adds VIP and PACAP to the only other neuropeptide, substance P, known to regulate TGF-beta1 production in immune cells.
Record Date Created: 20000621
Record Date Completed: 20000621

2/7/57 (Item 57 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2007 Dialog. All rts. reserv.

12610699 PMID: 10670826
(N-stearyl, norleucine17) VIP hybrid inhibits the growth of pancreatic cancer cell lines.
Zia H; Leyton J; Casibang M; Hau V; Brenneman D; Fridkin M; Gozes I; Moody T W
Cell and Cancer Biology Dept., Medicine Branch, National Cancer Institute, Rockville, MD 20850, USA.
Life sciences (ENGLAND) 2000, 66 (5) p379-87, ISSN 0024-3205--Print Journal Code: 0375521
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The effects vasoactive intestinal peptide (VIP) %antagonists% were investigated on pancreatic cancer cell lines. (N-Stearyl, Norleucine17) VIP hybrid ((SN)VIPhyb) inhibited 125I-VIP binding to human Capan-2 cells with an IC50 value of 0.01 microM whereas VIP hybrid had an IC50 value of 0.2 microM. By RT-PCR and Northern blot, %VPAC1% receptor mRNA was detected in CAPAN-2 cells. One microM (SN)VIPhyb and 10 microM VIPhyb inhibited the ability of 30 nM VIP to elevate cyclic AMP and increase c-fos mRNA. (SN)VIPhyb, 1 microM inhibited the clonal growth of CAPAN-2 cells in vitro. In vivo, (SN)VIPhyb (10 microg/day s.c.) inhibited CAPAN-2 xenograft growth in nude mice. These results indicate that (SN)VIPhyb is a pancreatic cancer VPAC receptor %antagonist%.
Record Date Created: 20000217
Record Date Completed: 20000217

2/7/58 (Item 58 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12593139 PMID: 10640731
Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit antigen-induced apoptosis of mature T lymphocytes by inhibiting Fas ligand expression.
Delgado M; Ganea D
Department of Biological Sciences, Rutgers University, Newark, NJ 07102, USA.
Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Feb 1 2000, 164 (3) p1200-10, ISSN 0022-1767--Print Journal Code: 2985117R
Contract/Grant No.: AI041786-02; AI; NIAID
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Apoptosis in T and B lymphocytes is a major element controlling the immune response. The Ag-induced cell death (AICD) in T cells is a main mechanism for maintaining peripheral tolerance and for limiting an ongoing immune response. AICD is initiated by Ag re-engagement of the TCR and is mediated through Fas/Fas ligand (FasL) interactions. Vasoactive intestinal peptide (VIP) and the structurally related pituitary adenylate cyclase-activating polypeptide (PACAP) are two multifunctional neuropeptides present in the lymphoid microenvironment that act primarily as anti-inflammatory agents. In the present study we investigated whether VIP and PACAP affect AICD in mature peripheral T cells and T cell hybridomas. VIP and PACAP reduce in a dose-dependent manner anti-CD3-induced apoptosis in Con A/IL-2-preactivated peripheral T cells and the murine T hybridomas 2B4.11 and A1.1. A functional study demonstrates that the inhibition of AICD is achieved through the inhibition of activation-induced FasL expression at protein and mRNA levels. VIP/PACAP-mediated inhibition of both AICD and FasL expression is mediated through the specific receptors %VPAC1% and VPAC2. Of obvious biological significance is the fact that VIP and PACAP prevent Ag-induced clonal deletion of CD4+ T cells, but not that of CD8+ T cells. By affecting FasL expression, VIP and PACAP may play a physiological role in both the generation of memory T cells and the inhibition of FasL-mediated T cell cytotoxicity.
Record Date Created: 20000224
Record Date Completed: 20000224

2/7/59 (Item 59 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12544481 PMID: 10491203
Vasoactive intestinal polypeptide %VPAC1% and VPAC2 receptor chimeras identify domains responsible for the specificity of ligand binding and activation.
Juarranz M G; Van Rampelbergh J; Gourlet P; De Neef P; Cnudde J; Robberecht P; Waelbroeck M
Department of Biochemistry and Nutrition, School of Medicine, Universite Libre de Bruxelles, Belgium.
European journal of biochemistry / FEBS (GERMANY) Oct 1 1999, 265 (1) p449-56, ISSN 0014-2956--Print Journal Code: 0107600
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
In order to identify the receptor domains responsible for the %VPAC1% selectivity of the VIP1 agonist, [Lys15, Arg16, Leu27] VIP (1-7)/GRF (8-27) and VIP1 %antagonist%, Ac His1 [D-Phe2, Lys15, Arg16, Leu27] VIP (3-7)/GRF (8-27), we evaluated their binding and functional properties on chimeric %VPAC1% /VPAC2 receptors. Our results suggest that the N-terminal extracellular domain is responsible for the selectivity of the VIP1 %antagonist% . Selective recognition of the VIP1 agonist was supported by a larger receptor area: in addition to the N-terminal domain, the first extracellular loop, as well as additional determinants in the distal part of the %VPAC1% receptor were involved. Furthermore, these additional domains were critical for an efficient receptor activation, as replacement of EC1 in %VPAC1% by its counter part in the VPAC2 receptor markedly reduced the maximal response.
Record Date Created: 19991122
Record Date Completed: 19991122

2/7/60 (Item 60 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12402748 PMID: 10337915
VIP and PACAP inhibit IL-12 production in LPS-stimulated macrophages. Subsequent effect on IFNgamma synthesis by T cells.
Delgado M; Munoz-Elias E J; Gomariz R P; Ganea D
Department of Biological Sciences, Rutgers University, Newark, NJ 07102-1811, USA. dganea@andromeda.rutgers.edu
Journal of neuroimmunology (NETHERLANDS) May 3 1999, 96 (2) p167-81, ISSN 0165-5728--Print Journal Code: 8109498
Contract/Grant No.: AI 41786-01; AI; NIAID
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Since IL-12 plays a central role against intracellular pathogens, and contributes to the pathogenesis of immune diseases, its regulation is essential. This study examines the effect of two neuropeptides, vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase activating polypeptide (PACAP), on interleukin-12 (IL-12) production. VIP/PACAP inhibit IL-12 dose-dependently. Type 1 VIP receptor (%VPAC1%), and to a lesser degree type 2 VIP receptor (VPAC2), mediate the inhibition of IL-12, primarily through the cAMP/PKA pathway. VIP/PACAP inhibit the production of IL-12, IL-6, tumor necrosis factor alpha (TNFalpha), and interferon gamma (IFNgamma) in vivo in endotoxemic mice. The presence of VIP/PACAP in the lymphoid organs and the specific effects on cytokine production offer a physiological basis for their immunomodulatory role in vivo.
Record Date Created: 19990603
Record Date Completed: 19990603

2/7/61 (Item 61 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12359781 PMID: 10202009
Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide prevent inducible nitric oxide synthase transcription in macrophages by inhibiting NF-kappa B and IFN regulatory factor 1 activation.
Delgado M; Munoz-Elias E J; Gomariz R P; Ganea D
Department of Biological Sciences, Rutgers University, Newark, NJ 07102, USA.
Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Apr 15 1999, 162 (8) p4685-96, ISSN 0022-1767--Print Journal Code: 2985117R
Contract/Grant No.: AI 41786-01; AI; NIAID
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
High-output nitric oxide (NO) production from activated macrophages, resulting from the induction of inducible NO synthase (iNOS) expression, represents a major mechanism for macrophage cytotoxicity against pathogens. However, despite its beneficial role in host defense, sustained high-output NO production was also implicated in a variety of acute inflammatory

diseases and autoimmune diseases. Therefore, the down-regulation of iNOS expression during an inflammatory process plays a significant physiological role. This study examines the role of two immunomodulatory neuropeptides, the vasoactive intestinal peptide (VIP) and the pituitary adenylate cyclase-activating polypeptide (PACAP), on NO production by LPS-, IFN-gamma-, and LPS/IFN-gamma-stimulated peritoneal macrophages and the Raw 264.7 cell line. Both VIP and PACAP inhibit NO production in a dose- and time-dependent manner by reducing iNOS expression at protein and mRNA level. %VPAC1%, the type 1 VIP receptor, which is constitutively expressed in macrophages, and to a lesser degree VPAC2, the type 2 VIP receptor, which is induced upon macrophage activation, mediate the effect of VIP/PACAP. VIP/PACAP inhibit iNOS expression and activity both in vivo and in vitro. Two transduction pathways appear to be involved, a cAMP-dependent pathway that preferentially inhibits IFN regulatory factor-1 transactivation and a cAMP-independent pathway that blocks NF-kappa B binding to the iNOS promoter. The down-regulation of iNOS expression, together with previously reported inhibitory effects on the production of the proinflammatory cytokines IL-6, TNF-alpha, and IL-12, and the stimulation of the anti-inflammatory IL-10, define VIP and PACAP as "macrophage deactivating factors" with significant physiological relevance.
Record Date Created: 19990506
Record Date Completed: 19990506

2/7/62 (Item 62 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12351362 PMID: 10193908
The role of VIP/PACAP receptor subtypes in spinal somatosensory processing in rats with an experimental peripheral mononeuropathy.
Dickinson T; Mitchell R; Robberecht P; Fleetwood-Walker S M
Department of Preclinical Veterinary Sciences, Royal (Dick) School of Veterinary Studies, University of Edinburgh, UK.
Neuropharmacology (ENGLAND) Jan 1999, 38 (1) p167-80, ISSN 0028-3908--Print Journal Code: 0236217
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Peripheral nerve damage often results in the development of chronic pain states, resistant to classical analgesics. Since vasoactive intestinal polypeptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) are up-regulated in dorsal root ganglion cells following peripheral nerve injury, we investigated the expression and influence of %VPAC1%, VPAC2 and PAC1 receptors in rat spinal dorsal horn following a chronic constriction injury (CCI). Electrophysiological studies revealed that selective %antagonists% of %VPAC1% , VPAC2 and PAC1 receptors inhibit mustard oil-, but not brush-induced activity of dorsal horn neurones in CCI animals, while cold-induced neuronal activity was attenuated by %VPAC1% and PAC1, but not VPAC2 receptor %antagonists% . Ionophoresis of selective agonists for the receptor subtypes revealed that the VPAC2 receptor agonist excited twice as many cells in CCI compared to normal animals, while the number of cells excited by the %VPAC1% receptor agonist decreased and responses to PACAP-38 remained unchanged. In situ hybridisation histochemistry (ISHH) confirmed an increase in the expression of VPAC2 receptor mRNA within the ipsilateral dorsal horn following neuropathy, while %VPAC1% receptor mRNA was seen to decrease and that for PAC1 receptors remained unchanged. These data indicate that VIP/PACAP receptors may be important regulatory factors in neuropathic pain states.
Record Date Created: 19990624
Record Date Completed: 19990624

2/7/63 (Item 63 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12344195 PMID: 10100920
Structural motifs of pituitary adenylate cyclase-activating polypeptide (PACAP) defining PAC1-receptor selectivity.
Schafer H; Zheng J; Morys-Wortmann C; Folsch U R; Schmidt W E
Laboratory of Molecular Gastroenterology and Hepatology, 1st Department of Internal Medicine, Christian-Albrechts-University of Kiel, Germany.
Regulatory peptides (NETHERLANDS) Feb 5 1999, 79 (2-3) p83-92, ISSN 0167-0115--Print Journal Code: 8100479
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Pituitary adenylate cyclase-activating polypeptide (PACAP) interacts with three types of PACAP/VIP-receptors. The PAC1-receptor accepts PACAP as a high affinity ligand but not vasoactive intestinal peptide (VIP) similarly binding to %VPAC1%- and VPAC2-receptors. To identify those amino acids not present in VIP defining PAC1-receptor selectivity of PACAP, radio receptor binding assays on AR4-2J cells were performed. It could be shown that PACAP(1-27) exhibited a distinct and much higher susceptibility to VIP-amino acid substitutions, compared to PACAP(1-38). Positions 4 and 5 seem to be most important for receptor binding of PACAP(1-27), whereas position 13 was identified to be crucial for maximal affinity of PACAP(1-38). PACAP(29-38) extension analogues of VIP revealed a stabilizing effect of the C-terminus of PACAP(1-38) on the optimal peptide conformation. The substitution analogues were also checked for their capacity to stimulate IP3 and cAMP formation in AR4-2J cells. Compared to PACAP(1-27) and PACAP(1-38), most analogues revealed potencies reduced congruously to their lower binding affinities. However, one of the analogues, PACAP(1-27) substituted in position 5, may represent a weak %antagonist% since this peptide was less potent in inducing second messengers than in label displacement. Our findings indicate that PACAP(1-27) and PACAP(1-38) differ in terms of their requirement of the amino acids in positions 4, 5, 9, 11 and 13 for maximal interaction with the PAC1-receptor.
Record Date Created: 19990528
Record Date Completed: 19990528

2/7/64 (Item 64 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12299359 PMID: 9973516
Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit endotoxin-induced TNF-alpha production by macrophages: in vitro and in vivo studies.
Delgado M; Pozo D; Martinez C; Leceta J; Calvo J R; Ganea D; Gomariz R P
Department of Cellular Biology, Faculty of Biology, Complutense University, Madrid, Spain.
Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Feb 15 1999, 162 (4) p2358-67, ISSN 0022-1767--Print Journal Code: 2985117R
Contract/Grant No.: AI41786; AI; NIAID
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Vasoactive intestinal peptide (VIP) is a neuropeptide synthesized by immune cells that can modulate several immune aspects, including the function of cells involved in the inflammatory response, such as macrophages and monocytes. The production and release of cytokines by activated phagocytes are important events in the pathogenesis of ischemia-reperfusion injury. There is abundant evidence that the proinflammatory cytokine TNF-alpha is an important mediator of shock and organ failure complicating Gram-negative sepsis. VIP has been shown to attenuate the deleterious consequences of this pathologic phenomenon. In this study we have investigated the effects of VIP and the structurally related neuropeptide pituitary adenylate cyclase-activating polypeptide (PACAP38) on the production of TNF-alpha by endotoxin-activated murine peritoneal macrophages. Both neuropeptides rapidly and specifically inhibit

the LPS-stimulated production of TNF-alpha, exerting their action through the binding to %VPAC1% receptor and the subsequent activation of the adenylate cyclase system. VIP and PACAP regulate the production of TNF-alpha at a transcriptional level. In vitro results were correlated with an inhibition of both TNF-alpha expression and release in endotoxemic mice in vivo. The immunomodulatory role of VIP in vivo is supported by the up-regulation of VIP release in serum and peritoneal fluid by LPS and proinflammatory cytokines such as TNF-alpha, IL-1beta, and IL-6. These findings support the idea that under toxicity conditions associated with high LPS doses, VIP and PACAP could act as protective mediators that regulate the excessive release of TNF-alpha to reduce inflammation or shock.
Record Date Created: 19990413
Record Date Completed: 19990413

2/7/65 (Item 65 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12299276 PMID: 9973433
Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide enhance IL-10 production by murine macrophages: in vitro and in vivo studies.
Delgado M; Munoz-Elias E J; Gomariz R P; Ganea D
Department of Biological Sciences, Rutgers University, Newark, NJ 07102, USA.
Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Feb 1 1999, 162 (3) p1707-16, ISSN 0022-1767--Print Journal Code: 2985117R
Contract/Grant No.: AI041786-01; AI; NIAID
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Vasoactive intestinal peptide (VIP), a neuropeptide present in the lymphoid microenvironment, and the structurally related pituitary adenylate cyclase-activating polypeptide (PACAP) act as potent anti-inflammatory agents that inhibit the function of activated macrophages and TH cells. Previous reports showed that VIP/PACAP inhibit IL-6 and TNF-alpha production in LPS-stimulated macrophages. The present study reports on the effect of VIP/PACAP on IL-10 production. Although VIP/PACAP do not induce IL-10 by themselves, they enhance IL-10 production in LPS-stimulated macrophages. The specific %VPAC1% receptor mediates the stimulatory effect of VIP/PACAP, and cAMP is the major second messenger involved. VIP/PACAP increase IL-10 mRNA in LPS-stimulated cells, and the effect of transcriptional and protein synthesis inhibitors indicates de novo IL-10 production. Electromobility shift assays show that VIP/PACAP induce an increase in nuclear cAMP response element (CRE)-binding complexes, with CRE binding protein as the major active component. Treatments with either a %VPAC1% %antagonist% or a protein kinase A inhibitor abolish IL-10 stimulation and, concomitantly, the increase in CRE binding. Effects similar to the in vitro stimulation of IL-10 were obtained in vivo in mice treated with LPS and VIP or PACAP. The neuropeptides induce increased levels of IL-10 in both serum and peritoneal fluid, and increased expression of the IL-10 mRNA in peritoneal exudate cells. The stimulation of IL-10 production in activated macrophages represents a novel anti-inflammatory activity of VIP and PACAP, which presumably acts in vivo in conjunction with the inhibition of proinflammatory cytokines such as IL-6 and TNF-alpha to reduce the magnitude of the immune response.
Record Date Created: 19990413
Record Date Completed: 19990413

2/7/66 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

18895998 BIOSIS NO.: 200600241393
Compositions and methods for treating ileus
AUTHOR: Gandhi Salil Atul
AUTHOR ADDRESS: Chicago, IL USA**USA
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents JUN 28 2005 2005
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The present invention is directed to compositions useful in treating or preventing ileus in a patient. The compositions of the invention include a pituitary adenylate cyclase activating peptide (PACAP) receptor %antagonist% and/or a vasoactive intestinal peptide (VIP) receptor %antagonist% in an amount sufficient to treat or prevent ileus in a patient. In one embodiment both a PACAP and VIP receptor %antagonists% are present, preferably in a combination that blocks vasoactive pituitary cyclase 1 (%VPAC1%), VPAC2 and pituitary adenylate cyclase 1 (PAC1) receptors. Methods of using such composition to treat or prevent ileus in a patient are also encompassed by the invention.

2/7/67 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

18355422 BIOSIS NO.: 200510049922
Arg (R) 188 in TM2, ASN (N) 229 in TM3 and GLN (Q) 380 in TM7 are key residues for activation of the human %VPAC1% receptor
AUTHOR: Nachtergael I (Reprint); Waelbroeck M; Langer I; Robberecht P
AUTHOR ADDRESS: Free Univ Brussels, Dept Biochem and Nutr, Fac Med, B-1070 Brussels, Belgium**Belgium
JOURNAL: Regulatory Peptides 122 (1): p33 SEP 30 04 2004
CONFERENCE/MEETING: 15th International Symposium on Regulatory Peptides Toulouse, FRANCE September 19 -22, 2004; 20040919
ISSN: 0167-0115
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

2/7/68 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

18230186 BIOSIS NO.: 200500136823
Human H9 cells proliferation is differently controlled by Vasoactive Intestinal Peptide or Peptide Histidine Methionine: implication of a GTP-insensitive form of VPAC, receptor
AUTHOR: Goursaud Stephanie; Pineau Nicolas; Becq-Giraudon Laetitia; Gressens Pierre; Muller Jean-Marc; Janet Thierry (Reprint)
AUTHOR ADDRESS: CNRSUMR 618, IPBC, 40 Ave Recteur Pineau,Pole Biol Sante, F-86022, Poitiers, France**France
AUTHOR E-MAIL ADDRESS: Thierry.Janet@univ-poitiers.fr
JOURNAL: Journal of Neuroimmunology 158 (1-2): p94-105 January 2005 2005
MEDIUM: print
ISSN: 0165-5728 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The proliferation of human lymphoblastoma cell line (H9) was differently stimulated by Peptide Histidine Methionine (PHM) and Vasoactive Intestinal Peptide (VIP). PHM induced a cyclic AMP (cAMP) accumulation, abolished by Adenylate Cyclase (AC) inhibitors leading to a loss of proliferative effect. VIP mitogenic activity was Pertussis toxin (PTX) sensitive and AC inhibitors insensitive. Pharmacological experiments performed on H9 membranes with or without a GTP analogue indicated expression of both GTP-insensitive and -sensitive PHM/VIP high-affinity binding sites (HA). H9 cells expressed only the %VPAC1% receptor. VIP(10-28), known as a %VPAC1% %antagonist%, bond to all

GTP-insensitive PHM sites and inhibited evenly the PHM and VIP mitogenic actions. These data strongly suggested different mechanisms initiated by VIP and PHM and highlighted the key role of GTP-insensitive binding sites in the control of cell proliferation. Copyright 2004 Elsevier B.V. All rights reserved.

2/7/69 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

18214492 BIOSIS NO.: 200500121557
A key role for transmembrane prolines in calcitonin receptor-like receptor agonist binding and signalling: Implications for family B G-protein-coupled receptors
AUTHOR: Conner Alex C; Hay Debbie L; Simms John; Howitt Stephen G; Schindler Marcus; Smith David M; Wheatley Mark; Poyner David R (Reprint)
AUTHOR ADDRESS: Sch Life and Hlth Sci, Aston Univ, Birmingham, W Midlands, B4 7ET, UK**UK
AUTHOR E-MAIL ADDRESS: d.r.poyner@aston.ac.uk
JOURNAL: Molecular Pharmacology 67 (1): p20-31 January 2005 2005
MEDIUM: print
ISSN: 0026-895X _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Calcitonin receptor like-receptor is a family B G-protein coupled receptor (GPCR). It requires receptor activity modifying protein (RAMP) 1 to give a calcitonin gene-related peptide (CGRP) receptor. Little is known of how members of this receptor family function. Proline residues often form important kinks in alpha-helices. Therefore, all proline residues within the transmembrane helices of the receptor (Pro241, Pro244 in helix 4, Pro275 in helix 5, Pro321 and Pro331 in helix 6) were mutated to alanine. Pro241, Pro275, and Pro321 are highly conserved throughout all family B GPCRs. The binding of CGRP and its ability to stimulate cAMP production were investigated in mutant and wild-type receptors after transient transfection into COS-7 cells with RAMP1. The P321A mutation significantly decreased the pEC50 for CGRP and reduced its affinity but did not change cell-surface expression. %Antagonist% binding (CGRP8-37 and 1-piperidinecarboxamide, N-(2-((5amino-1-((4-(4-pyridinyl)-1-piperazinyl) carbonyl) pentyl)amino)-1-((3,5-dibromo-4-hydroxyphenyl) methyl)-2-oxoethyl)-4-(1,4-dihydro-2-oxo-3(2H)-quinazolinyl) (BIBN4096BS)) was little altered by the mutation. Adrenomedullin-mediated signaling was disrupted when P321A was coexpressed with RAMP1, RAMP2, or RAMP3. The P331A mutant produced a moderate reduction in CGRP binding and receptor activation. Mutation of the other residues had no effect on receptor function. Thus, Pro321 and Pro331 are required for agonist binding and receptor activation. Modeling suggested that Pro321 induces a bend in helix 6, bringing its C terminus near that of helix 3, as seen in many family A GPCRs. This is abolished in P321A. P321A-I325P, predicted to restore this conformation, showed wild-type activation. Modeling can also rationalize the effects of transmembrane proline mutants previously reported for another family B GPCR, the %VPAC1% receptor.

2/7/70 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

18083612 BIOSIS NO.: 200400464841
Inhibitory pathways in the circular muscle of rat jejunum
AUTHOR: Vanneste Gwen; Robberecht Patrick; Lefebvre Romain A (Reprint)
AUTHOR ADDRESS: Heymans Inst Pharmacol, Ghent Univ, De Pintelaan 185, B-9000, Ghent, Belgium**Belgium
AUTHOR E-MAIL ADDRESS: romain.lefebvre@UGent.be
JOURNAL: British Journal of Pharmacology 143 (1): p107-118 September 2004 2004
MEDIUM: print
ISSN: 0007-1188 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: 1 Conflicting data have been reported on the contribution of nitric oxide (NO) to inhibitory neurotransmission in rat jejunum. Therefore, the mechanism of relaxation and contribution to inhibitory neurotransmission of NO, adenosine 5'- triphosphate (ATP), vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating peptide (PACAP) was examined in the circular muscle of Wistar - Han rat jejunum. 2 Mucosa-free circular muscle strips were precontracted with methacholine in the presence of guanethidine and exposed to electrical field stimulation (EFS) and exogenous NO, ATP, VIP and PACAP. All stimuli induced reduction of tone and inhibition of phasic motility. Only electrically induced responses were sensitive to tetrodotoxin (3 x 10-6 M). 3 NO (10-6 - 10-4 M)-induced concentration-dependent relaxations that were inhibited by the soluble guanylyl cyclase inhibitor 1H-(1,2,4)-oxadiazolo-(4,3-a)-quinoxalin-1-one (ODQ; 10-5 M) and the small conductance Ca2+-activated K+-channel blocker apamin (APA; 3 x 10-8 M). 4 Relaxations elicited by exogenous ATP (10-4 - 10-3 M) were inhibited by the P2Y purinoceptor %antagonist% reactive blue 2 (RB2; 3 x 10-4 M), but not by APA and ODQ. 5 The inhibitory responses evoked by 10-7 M VIP and 3 x 10-8 M PACAP were decreased by the selective PAC1 receptor %antagonist% PACAP6-38 (3 x 10-6 M) and APA. The VPAC2 receptor %antagonist% PG99-465 (3 x 10-7 M) reduced relaxations caused by VIP, but not those by PACAP, while the %VPAC1% receptor %antagonist% PG97-269 (3 x 10-7 M) had no influence. 6 EFS-induced relaxations were inhibited by the NO-synthase inhibitor Nomega-nitro-L-arginine methyl ester (3 x 10-4 M), ODQ and APA, but not by RB2, PG97-269, PG99-465 and PACAP6-38. 7 These results suggest that NO is the main inhibitory neurotransmitter in the circular muscle of Wistar - Han rat jejunum acting through a rise in cyclic guanosine monophosphate levels and activation of small conductance Ca2+-dependent K+ channels.

2/7/71 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

17965101 BIOSIS NO.: 200400335890
Circadian rhythm in inhibitory synaptic transmission in the mouse suprachiasmatic nucleus
AUTHOR: Itri Jason; Michel Stephan; Waschek James A; Colwell Christopher S (Reprint)
AUTHOR ADDRESS: Mental Retardat Res CtrDept Psychiat and Biobehav Sci, Univ Calif Los Angeles, 760 Westwood Plaza, Los Angeles, CA, 90024, USA**USA
AUTHOR E-MAIL ADDRESS: ccolwell@mednet.ucla.edu
JOURNAL: Journal of Neurophysiology (Bethesda) 92 (1): p311-319 July 2004 2004
MEDIUM: print
ISSN: 0022-3077 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: It is widely accepted that most suprachiasmatic nucleus (SCN) neurons express the neurotransmitter GABA and are likely to use this neurotransmitter to regulate excitability within the SCN. To evaluate the possibility that inhibitory synaptic transmission varies with a circadian rhythm within the mouse SCN, we used whole cell patch-clamp recording in an acute brain slice preparation to record GABA-mediated spontaneous inhibitory postsynaptic currents (sIPSCs). We found that the sIPSC frequency in the dorsal SCN (dSCN) exhibited a TTX-sensitive daily rhythm that peaked during the late day and early night in mice held in a light: dark cycle. We next evaluated whether vasoactive intestinal peptide (VIP) was responsible for the observed rhythm in IPSC frequency. Pretreatment of SCN slices with %VPAC1%/ VPAC2- or VPAC2-specific receptor %antagonists% prevented the increase in sIPSC frequency in the dSCN. The rhythm in sIPSC frequency was absent in VIP/peptide histidine

isoleucine (PHI)-deficient mice. Finally, we were able to detect a rhythm in the frequency of inhibitory synaptic transmission in mice held in constant darkness that was also dependent on VIP and the VPAC2 receptor. Overall, these data demonstrate that there is a circadian rhythm in GABAergic transmission in the dorsal region of the mouse SCN and that the VIP is required for expression of this rhythm.

2/7/72 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

17779421 BIOSIS NO.: 200400146082
Muscarinic m4 and PACAP receptor interaction in the rat nucleus accumbens.
AUTHOR: Onali P (Reprint); Mascia F M (Reprint); Garau L (Reprint); Olianas M C (Reprint)
AUTHOR ADDRESS: Section of BioChem. Pharmacol., Dept. of Neurosci., Univ. of Cagliari, Cagliari, Italy**Italy
JOURNAL: Society for Neuroscience Abstract Viewer and Itinerary Planner 2003 pAbstract No. 799.20 2003 2003
MEDIUM: e-file
CONFERENCE/MEETING: 33rd Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 08-12, 2003; 20031108
SPONSOR: Society of Neuroscience
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The rat nucleus accumbens expresses muscarinic cholinergic and pituitary adenylyl cyclase-activating polipeptide (PACAP) receptors, which are both involved in the control of psychomotor stimulation and emotional behavior. In the present study we have investigated the possible interaction between these two neurotransmitter receptor systems by examining their effects on cyclic AMP production. In a tissue membrane preparation, PACAP38 and PACAP27 elicited a concentration-dependent stimulation of adenylyl cyclase activity with nanomolar potencies, whereas vasoactive intestinal peptide (VIP) and (Ala11,22,28)VIP, a selective %VPAC1% receptor agonist, were much less potent.Moreover, the PACAP receptor %antagonist% PACAP 6-38 blocked the PACAP38 stimulatory effect with a Ki value of about 15 nM. The addition of carbachol caused a concentration-dependent inhibition of PACAP38-stimulated adenylyl cyclase activity with an EC50 value of 0.4 muM. The inhibitory effect of carbachol was antagonized by the selective muscarinic M4 receptor %antagonist% MT3 with a Ki of about 7 nM. These data indicate that in nucleus accumbens PACAP and muscarinic M4 receptors %antagonistically% interact in the control of cyclic AMP formation likely through the localization on common neuronal elements.

2/7/73 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

17775231 BIOSIS NO.: 200400155988
Heterogeneity of neuronal and smooth muscle receptors involved in the VIP- and PACAP-induced relaxations of the pig intravesical ureter.
AUTHOR: Hernandez Medardo (Reprint); Barahona Maria Victoria; Recio Paz; Rivera Luis; Benedito Sara; Martinez Ana Cristina; Garcia-Sacristan Albino; Orensanz Luis M; Prieto Dolores
AUTHOR ADDRESS: Departamento de Fisiologia, Facultad de Farmacia, UCM, 28040, Madrid, Spain**Spain
AUTHOR E-MAIL ADDRESS: medardo@vet.ucm.es
JOURNAL: British Journal of Pharmacology 141 (1): p123-131 January 2004 2004
MEDIUM: print
ISSN: 0007-1188 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: 1 The mechanisms and receptors involved in the vasoactive intestinal peptide (VIP)- and pituitary adenylate cyclase-activating polypeptide (PACAP)-induced relaxations of the pig intravesical ureter were investigated. 2 VIP, PACAP 38 and PACAP 27 concentration-dependently relaxed U46619-contracted ureteral strips with a similar potency. (Ala11,22,28)-VIP, a %VPAC1% agonist, showed inconsistent relaxations. 3 The neuronal voltage-gated Ca2+ channel inhibitor, omega-conotoxin GVIA (omega-CgTX, 1 muM), reduced the VIP relaxations. Urothelium removal or blockade of capsaicin-sensitive primary afferents, nitric oxide (NO) synthase and guanylate cyclase with capsaicin (10 muM), NG-nitro-L-arginine (L-NOARG, 100 muM) and 1H-(1,2,4)-oxadiazolo(4,3-a)quinoxalin-1-one (ODQ, 5 muM), respectively, did not change the VIP relaxations. However, the PACAP 38 relaxations were reduced by omega-CgTX, capsaicin, L-NOARG and ODQ. 4 The VIP and VIP/PACAP receptor %antagonists%, (Lys1, Pro2,5, Arg3,4, Tyr6)-VIP (1 muM) and PACAP (6-38) (0.4 muM), inhibited VIP and VIP and PACAP 38, respectively, relaxations. 5 The nonselective and large-conductance Ca2-activated K+ channel blockers, tetraethylammonium (3 mM) and charybdotoxin (0.1 muM), respectively, and neuropeptide Y (0.1 muM) did not modify the VIP relaxations. The small-conductance Ca2-activated K+ channel blocker apamin (1 muM) did not change the PACAP 27 relaxations. 6 The cAMP-dependent protein kinase A (PKA) blocker, 8-(4-chlorophenylthio)adenosine-3',5'-cyclic monophosphorothioate (Rp-8-CPT-cAMPS, 100 muM), reduced VIP relaxations. The phosphodiesterase 4 inhibitor rolipram and the adenylate cyclase activator forskolin relaxed ureteral preparations. The rolipram relaxations were reduced by Rp-8-CPT-cAMPS. Forskolin (30 nM) evoked a potentiation of VIP relaxations. 7 These results suggest that VIP and PACAP relax the pig ureter through smooth muscle receptors, probably of the VPAC2 subtype, linked to a cAMP-PKA pathway. Neuronal VPAC receptors localized at motor nerves and PAC1 receptors placed at sensory nerves and coupled to NO release, seem also to be involved in the VIP and PACAP 38 relaxations.

2/7/74 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

17415263 BIOSIS NO.: 200300373982
Localisation of VIP-binding sites exhibiting properties of VPAC receptors in chromaffin cells of rainbow trout (Oncorhynchus mykiss).
AUTHOR: Montpetit Colin J; Shahsavarani Arash; Perry Steve F (Reprint)
AUTHOR ADDRESS: Department of Biology, University of Ottawa, 30 Marie Curie, Ottawa, ON, K1N 6N5, Canada**Canada
AUTHOR E-MAIL ADDRESS: sfperry@science.uottawa.ca
JOURNAL: Journal of Experimental Biology 206 (11): p1917-1927 June 2003 2003
MEDIUM: print
ISSN: 0022-0949 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The current model for the neuronal control of catecholamine release from piscine chromaffin cells advocates that the neurotransmitters vasoactive intestinal polypeptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) are co-released with acetylcholine from preganglionic fibres upon nerve stimulation. Both VIP and PACAP elicit the secretion of exclusively adrenaline from rainbow trout chromaffin cells, which presumably arises from the activation of VPAC type receptors. Thus, the goals of the present study were (1) to localise VPAC receptors in the chromaffin cell fraction of the posterior cardinal vein (PCV) of trout and (2) to test the hypothesis that the selective secretion of adrenaline elicited by VIP could be explained by the absence of the VPAC receptors from the noradrenaline-containing cells. Fluorescent labelling of chromaffin cells using aldehyde-induced fluorescence of catecholamines and antisera raised against dopamine beta-hydroxylase (DbetaH) revealed a distinct layer of chromaffin cells lining the walls of the PCV. Furthermore, specific VIP-binding sites were demonstrated on chromaffin cells using a biotinylated VIP that was

previously established as being bioactive. Although multiple labelling experiments revealed that a number of DbetaH-positive cells were immunonegative for phenylethanolamine N-methyl transferase (PNMT; noradrenaline-containing cells versus adrenaline-containing cells, respectively), labelling of VIP-binding sites was similar to that of DbetaH labelling, suggesting that all chromaffin cells possess VIP-binding sites. Pharmacological assessment of the VIP-binding sites indicated that they exhibited characteristics of VPAC receptors. Specifically, the labelling of VIP-binding sites was prevented after pre-treatment of PCV tissue sections with unlabelled VIP, PACAP or the specific VPAC receptor %antagonist% VIP 6-28. By contrast, sections pre-treated with the PAC1 receptor blocker PACAP 6-27 displayed normal labelling of VIP-binding sites. Finally, partial cDNA clones for the trout %VPAC1% and VPAC2 receptor were obtained and sequenced. Tissue distribution experiments using RT-PCR revealed the presence of %VPAC1% receptor mRNA but not that of the VPAC2 receptor in the PCV tissue. The results provide direct evidence that VIP and PACAP can elicit the secretion of adrenaline from the chromaffin tissue via specific VIP-binding sites that exhibit properties of VPAC receptors. However, the selective secretion of adrenaline by VIP or PACAP cannot be explained by a lack of VIP-binding sites on the noradrenaline-containing cells.

2/7/75 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

17315963 BIOSIS NO.: 200300270496
Helospectin I and II evoke VIP and PACAP1-38 receptor-independent vasodilation in vivo.
AUTHOR: Rubinstein Israel (Reprint); Tsueshita Takaya; Gandhi Salil; Onyuksel Hayat
AUTHOR ADDRESS: Medicine, University of Illinois at Chicago, 840 S. Wood Street, M/C 719, Chicago, IL, 60612, USA**USA
AUTHOR E-MAIL ADDRESS: irubinst@uic.edu; tsueshita@aol.com; salilgandhi@vipogen.com; hayat@uic.edu
JOURNAL: FASEB Journal 17 (4-5): pAbstract No. 399.9 March 2003 2003
MEDIUM: e-file
CONFERENCE/MEETING: FASEB Meeting on Experimental Biology: Translating the Genome San Diego, CA, USA April 11-15, 2003; 20030411
SPONSOR: FASEB
ISSN: 0892-6638 _(ISSN print)
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Helospectin I and II, 2 peptides of the glucagons/secretin/vasoactive intestinal pepide (VIP) superfamily of peptides, elicit potent relaxation of pulmonary artery smooth muscle. However, the mechanisms underlying this response are uncertain. The purpose of this study was to begin to address this issue by determining whether the vasorelaxant effects of helospectin I and II are mediated by VIP and pituitary adenylate cyclase activating peptide (PACAP1-38) receptors in vivo. Using intravital microscopy, we found that suffusion of helospectin I and II (each, 0.1, 1& 10 mol) evoked significant concentration-dependent vasodilation of similar magnitude in the intact hamster cheek pouch microcirculation (p<0.05). Pretreatment with VIP10-28, a %VPAC1%/VPAC2 receptors %antagonist%, and PACAP6-38, a PAC1/VPAC2 receptor %antagonist%, had no significant effects on helospectin-induced vasodilation. In addition, indomethacin had no significant effects on helospectin-induced responses. Taken together, these data indicate that the vasorelaxant effects of helospectins I and II in the intact peripheral microcirculation are not mediated by activation of VIP and PACAP1-38 receptors nor vasodilatory prostaglandins.

2/7/76 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

17230105 BIOSIS NO.: 200300188824
VIP as a trophic factor in the CNS and cancer cells.
AUTHOR: Moody Terry W (Reprint); Hill Joanna M; Jensen Robert T
AUTHOR ADDRESS: NCI Office of the Director, Center for Cancer Research, National Cancer Institute, 31 Center Dr., Bldg. 31, Rm. 3A34, Bethesda, MD, USA**USA
AUTHOR E-MAIL ADDRESS: moodyt@mail.nih.gov
JOURNAL: Peptides (New York) 24 (1): p163-177 January 2003 2003
MEDIUM: print
ISSN: 0196-9781
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The effects of vasoactive intestinal peptide (VIP) on the proliferation of central nervous system (CNS) and cancer cells were investigated. VIP has important actions during CNS development. During neurogenesis, VIP stimulates the proliferation and differentiation of brain neurons. Addition of VIP to embryonic mouse spinal cord cultures increases neuronal survival and activity dependent neurotrophic factor (ADNF) secretion from astroglial cells. VIP is an integrative regulator of brain growth and development during neurogenesis and embryogenesis. Also, VIP causes increased proliferation of human breast and lung cancer cells in vitro. VIP binds with high affinity to cancer cells, elevates the cAMP and increases gene expression of c-fos, c-jun, c-myc and vascular endothelial cell growth factor. The effects of VIP on cancer cells are reversed by VIPhybrid, a synthetic %VPAC1% receptor %antagonist%. VIPhyb inhibits the basal growth of lung cancer cells in vitro and tumors in vivo and potentiates the ability of chemotherapeutic drugs to kill cancer cells. Due to the high density of %VPAC1% receptors in cancer cells, VIP has been radiolabeled with 123I, 18F and 99mTc to image tumors. It remains to be determined if radiolabeled VIP analogs will be useful agents for early detection of cancer in patients.

2/7/77 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

17220806 BIOSIS NO.: 200300179525
Pharmacological evidence suggests that the lysozyme/PACAP receptor of Tetrahymena thermophila is a polycation receptor.
AUTHOR: Keedy Michael; Yorgey Nathan; Hilty Jeremy; Price Angela; Hassenzahl David; Kuruvilla Heather (Reprint)
AUTHOR ADDRESS: Department of Science and Mathematics, Cedarville University, 251 North Main St., Cedarville, OH, 45314, USA**USA
AUTHOR E-MAIL ADDRESS: kuruvilh@cedarville.edu
JOURNAL: Acta Protozoologica 42 (1): p11-17 February 2003 2003
MEDIUM: print
ISSN: 0065-1583
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Pituitary adenylate cyclase activating polypeptide (PACAP) is a peptide hormone that exists in two biologically active forms: PACAP-38 and PACAP-27. Several types of PACAP receptors have been characterized, and these have been classified into three families: the %VPAC1%, the VPAC2, and the PAC1 receptors. In this study, we used in vivo behavioral assays along with pharmacological inhibitors to investigate the behavior of the lysozyme/PACAP receptor in Tetrahymena. This receptor behaves like a PAC1 receptor in some respects; however, PACAP 6-38 serves as an agonist, rather than an %antagonist%, for this receptor. These results are consistent with the existence of a generalized polycation receptor rather than a PACAP-specific receptor.

2/7/78 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

17075543 BIOSIS NO.: 200300034262
PACAP-27 tyrosine phosphorylates mitogen activated protein kinase and increases VEGF mRNAs in human lung cancer cells.
AUTHOR: Moody Terry W (Reprint); Leyton Julius; Casibang Marchessini; Pisegna Joseph; Jensen Robert T
AUTHOR ADDRESS: Office of the Director, Center for Cancer Research, National Cancer Institute, 31 Center Drive, Bldg. 31, Rm. 3A34, Bethesda, MD, 20892, USA**USA
AUTHOR E-MAIL ADDRESS: moodyt@mail.nih.gov
JOURNAL: Regulatory Peptides 109 (1-3): p135-140 15 November, 2002 2002
MEDIUM: print
ISSN: 0167-0115 _(ISSN print)
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The effects of pituitary adenylate cyclase activating polypeptide (PACAP) on human lung cancer cell line NCI-1299 mitogen activated protein kinase (MAPK) tyrosine phosphorylation and vascular endothelial cell growth factor (VEGF) expression were investigated. PACAP-27 (100 nM) increased MAPK tyrosine phosphorylation 3-fold, 5 min after addition to NCI-H1299 cells. PACAP caused tyrosine phosphorylation in a concentration-dependent manner being half-maximal at 10 nM PACAP-27. PACAP-27 or PACAP-38 (100 nM) but not PACAP28-38 or VIP caused increased MAPK tyrosine phosphorylation using NCI-H1299 cells. Also, the increase in MAPK tyrosine phosphorylation caused by PACAP-27 was totally inhibited by 10 muM PACAP(6-38), a PAC1 receptor %antagonist% or 10 muM PD98059, a MAPKK inhibitor. These results suggest that PAC1 receptors regulate tyrosine phosphorylation of MAPK in a MAPKK-dependent manner. PACAP-27 (100 nM) caused increased VEGF mRNA in NCI-H1299 cells after 8 h. The increase in VEGF mRNA caused by PACAP-27 was partially inhibited by PACAP(6-38), PD98059 and H-89. Addition of VIP to NCI-H1299 cells caused increased VEGF mRNA, which was totally inhibited by H89, a PKA inhibitor. These results suggest that PAC1 and %VPAC1% receptors regulate VEGF expression in lung cancer cells.

2/7/79 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

16965214 BIOSIS NO.: 200200558725
Lysine 195 and aspartate 196 of the first extracellular loop of the %VPAC1% receptor are essential for high affinity binding of agonist but not of %antagonist%
AUTHOR: Langer I (Reprint); Vertongen P (Reprint); Perret J (Reprint); Waelbroeck M (Reprint); Robberecht P (Reprint)
AUTHOR ADDRESS: Department of Biological Chemistry and Nutrition, Faculty of Medicine, Universite Libre de Bruxelles, Brussels, Belgium**Belgium
JOURNAL: Regulatory Peptides 108 (1): p13 15 August, 2002 2002
MEDIUM: print
CONFERENCE/MEETING: 14th International Symposium on Regulatory Peptides Boston, MA, USA August 31-September 03, 2002; 20020831
ISSN: 0167-0115
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

2/7/80 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

16887782 BIOSIS NO.: 200200481293
Two tyrosine residues in the first transmembrane helix of the human vasoactive intestinal peptide receptors play a role in supporting the active conformation
AUTHOR: Perret J; Vertongen P; Solano R M; Langer I; Cnudde J; Robberecht P ; Waelbroeck M (Reprint)
AUTHOR ADDRESS: Department of Biochemistry and Nutrition, School of Medicine, Universite Libre de Bruxelles, 808 Route de Lennik, Bat G/E, B-1070, CP 611, Bruxelles, Belgium**Belgium
JOURNAL: British Journal of Pharmacology 136 (7): p1042-1048 August, 2002 2002
MEDIUM: print
ISSN: 0007-1188
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: 1 We investigated the human vasoactive intestinal polypeptide (VIP) receptors %VPAC1% and VPAC2 mutated at conserved tyrosine residues in the first transmembrane helix (%VPAC1% receptor Y146A and Y150A and VPAC2 receptor Y130A and Y134A). 2 (125I)-Acetyl-His1 (D-Phe2, K15, R16, L27)-VIP (1-7)/GRF (8-27) (referred to as (125I)-%VPAC1% %antagonist%) labelled %VPAC1% binding sites, that displayed high and low affinities for VIP (IC50 values and per cent of high affinity binding sites: wild-type, 1 nM (57+-9%) and 160 nM; Y146A, 30 nM (40+-8%) and 800 nM; Y150A, 4 nM (27+-8%) and 300 nM). (R16)-VIP behaved as a 'super agonist' at both mutated %VPAC1% receptors and the efficacies of VIP analogues modified in positions 1, 3 and 6 were significantly decreased. 3 VIP was less potent at the Y130A and Y134A mutated VPAC2 receptors (EC50 200 and 400 nM, respectively) than at the wild-type VPAC2 receptor (EC50 7 nM). Furthermore, (hexanoyl-His1)-VIP behaved as a 'super agonist' at the two mutated VPAC2 receptors, and VIP analogues modified in positions 1, 3 and 6 were less potent and efficient at the mutated than at wild-type VPAC2 receptors. However, the Y130A and Y134A mutants could not be studied in binding assays 4 Our results suggest that the conserved tyrosine residues do not interact directly with the VIP His1, Asp3 or Phe6 residues (that are necessary for receptor activation), but stabilize the correct active receptor conformation.

2/7/81 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

16808025 BIOSIS NO.: 200200401536
Expression and function of vasoactive intestinal peptide, pituitary adenylate cyclase-activating polypeptide, and their receptors in the human adrenal gland
AUTHOR: Mazzocchi G; Malendowicz L K; Rebuffat P; Gottardo L; Nussdorfer Gastone G (Reprint)
AUTHOR ADDRESS: Department of Human Anatomy and Physiology, Section of Anatomy, Via Gabelli 65, I-35121, Padova, Italy**Italy
JOURNAL: Journal of Clinical Endocrinology and Metabolism 87 (6): p 2575-2580 June, 2002 2002
MEDIUM: print
ISSN: 0021-972X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: VIP and pituitary adenylate cyclase-activating polypeptide (PACAP) are two regulatory peptides that possess remarkable amino acid sequence homology and act through common receptors, named PAC1, %VPAC1%, and VPAC2. PAC1 receptor is selective for PACAP, whereas %VPAC1% and VPAC2 receptors bind both VIP and PACAP. We have investigated the expression and function of VIP, PACAP, and their receptors in the zona glomerulosa (ZG), zonae fasciculata and reticularis, and adrenal medulla (AM) of the human adrenal cortex. RT-PCR and RIA detected VIP and PACAP expression exclusively in AM cells. RT-PCR demonstrated the presence of PAC1 mRNA only in AM and of %VPAC1% and VPAC2 mRNAs in both ZG and AM cells. VIP and PACAP concentration-dependently increased aldosterone and catecholamine secretion from cultured ZG and AM cells. The catecholamine response to both peptides was higher than the aldosterone response, and the secretagogue action of PACAP was more intense than that of VIP. The aldosterone response of cultured ZG cells to VIP or PACAP was unaffected

by the PAC1 receptor %antagonist% PACAP-(6-38) (PAC1-A), but was significantly decreased by the %VPAC1% receptor %antagonist% (Ac-His1,D-Phe2,Lys15, Arg16)VIP-(3-7),GH-releasing factor-(8-27)-NH2 (%VPAC1%-A). The catecholamine response of cultured AM cells to VIP was lowered by %VPAC1%-A and unaffected by PAC1-A; conversely, the catecholamine response to PACAP was reduced by both PAC1-A and %VPAC1%-A. Simultaneous exposure to both %antagonists% did not abolish the catecholamine response to PACAP. Collectively, our findings allow us to conclude that in human adrenals 1) VIP and PACAP biosynthesis exclusively occurs in AM cells; 2) ZG cells are provided with functional %VPAC1% and VPAC2 receptors, whose activation by VIP or PACAP elicits a moderate aldosterone response; 3) AM cells possess PAC1, %VPAC1%, and VPAC2 receptors, whose activation evokes a marked catecholamine response; and 4) the catecholamine response to PACAP is more intense than that to VIP, because it is mediated by all subtypes of VIP/PACAP receptors.

2/7/82 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

16786655 BIOSIS NO.: 200200380166
%VPAC1% receptors have different agonist efficacy profiles on membrane and intact cells
AUTHOR: Langer Ingrid (Reprint); Vertongen Pascale; Perret Jason; Cnudde Johnny; Gregoire Francoise; De Neef Philippe; Robberecht Patrick; Waelbroeck Magali
AUTHOR ADDRESS: Department of Biological Chemistry and Nutrition, Faculty of Medicine, Universite Libre de Bruxelles, 808 Route de Lennik, Bat GE, B-1070, CP 611, Brussels, Belgium**Belgium
JOURNAL: Cellular Signalling 14 (8): p689-694 August, 2002 2002
MEDIUM: print
ISSN: 0898-6568
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The vasoactive intestinal peptide receptor %VPAC1% is preferentially coupled to Galphas protein but also increases (Ca2+)i through interaction with Galphai/Galphaq protein. We evaluated a panel of full, partial and null agonists for their capability to stimulate adenylate cyclase activity in both intact cells and membrane and (Ca2+)i in intact cells transfected with the reporter gene aequorin. In intact cells, the agonists efficacy for cAMP and calcium increase were well, but not linearly correlated: %VPAC1% receptors activated Galphas protein more efficiently but with the same pharmacological profile as the other G proteins. In contrast, there was a difference between cAMP increase in intact and broken cell membranes: EC50 values were generally lower in intact cells whereas the efficacy was higher. There was, however, no correlation between the shift in the EC50 value and the intrinsic activity. Of interest, the (4-28) fragment, a reported %antagonist% on cell membrane, was a full agonist in intact cells. We concluded that the active states of the %VPAC1% receptor resulting from the coupling to different effector are undistinguishable by the VIP analogs tested but that receptor properties are different when evaluated in intact cells or cell membranes.

2/7/83 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

16667597 BIOSIS NO.: 200200261108
Elucidation of vasoactive intestinal peptide pharmacophore for %VPAC1% receptors in human, rat, and guinea pig
AUTHOR: Igarashi Hisato; Ito Tetsuhide; Hou Wei; Mantey Samuel A; Pradhan Tapas K; Ulrich Charles D II; Hocart Simon J; Coy David H; Jensen Robert T (Reprint)
AUTHOR ADDRESS: Digestive Diseases Branch, National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases, 10 Center Dr., Bldg. 10, Rm. 9C-103, Bethesda, MD, 20892-1804, USA**USA
JOURNAL: Journal of Pharmacology and Experimental Therapeutics 301 (1): p 37-50 April, 2002 2002
MEDIUM: print
ISSN: 0022-3565
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Vasoactive intestinal peptide (VIP) is a neurotransmitter involved in a number of pathological and physiological processes. VIP is rapidly degraded and simplified stable analogs are needed. VIP's action was extensively studied in rat and guinea pig. However, it is largely unknown whether its pharmacophore in these species resembles human. To address this issue we investigated the VIP pharmacophore for %VPAC1% (the predominant receptor subtype in cancers and widely distributed in normal tissues) by using alanine and D-amino acid scanning. Interaction with rat, guinea pig, and human %VPAC1% was assessed using transfected Chinese hamster ovary (CHO) and PANC1 cells and cells possessing native %VPAC1%. Important species differences existed in the VIP pharmacophore. The human %VPAC1% expressed in CHO cells, which were used almost exclusively in previous studies, differed markedly from the native %VPAC1% in T47D cells. The most important amino acids for determining affinity are His1, Asp3, Phe6, Arg12, Arg14, and Leu23. Ser2, Asp8, Asn9, Thr11, Val19, Asn24, Ser25, Leu27, and Asn28 are not essential for high-affinity interaction/activation. (Ala2,8,9,11,19,24,25,27,28)VIP, which contained 11 alanines, was synthesized and it was equipotent to VIP at %VPAC1% receptors in all species and was metabolically stable. Our results show in any design of simplified VIP analogs for %VPAC1% it will be important to consider species differences and it is essential to use transfected systems that reflect the native receptor's pharmacophore. Last, with our results a simplified, metabolically stable VIP analog was identified that should be useful as a prototype for design of selective agonists/ %antagonists% that could be useful therapeutically.

2/7/84 (Item 19 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

16555095 BIOSIS NO.: 200200148606
Characterization of functional VIP/PACAP receptors in the human erythroleukemic HEL cell line
AUTHOR: Lema-Kisoka Roger; Hayez Nathalie; Langer Ingrid; Robberecht Patrick; Sariban Eric; Delporte Christine (Reprint)
AUTHOR ADDRESS: Department of Biochemistry and Nutrition, Faculty of Medicine, Universite Libre de Bruxelles, Brussels, Belgium**Belgium
JOURNAL: Peptides (New York) 22 (12): p2155-2162 December, 2001 2001
MEDIUM: print
ISSN: 0196-9781
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The presence of VIP/PACAP receptors was investigated on the human erythroleukemic cell line HEL. Specific binding of (125I)-PACAP or (125I)-VIP on HEL cells or membranes was very low and did not allow to perform competition curves. At 37degreeC PACAP transiently increased cAMP levels in the presence of the non-specific phosphodiesterase inhibitor IBMX, suggesting rapid desensitization. Kinetic studies revealed that optimal conditions to measure the EC50 of PACAP(1-27) were 10 min at 20degreeC. Under those conditions, PACAP-related peptides increased cAMP levels with EC50 in agreement with the pharmacological profile of the %VPAC1% receptor subtype: PACAP = VIP > (K15 R16 L27)VIP(1-7)/GRF(8-27) = (R16)ChSn (two %VPAC1% agonists) mchgt helodermin = secretin. RO 25-1553, a selective activator of VPAC2 receptor was inactive at 1 muM. Dose-response curves of %VPAC1% agonist molecules (PACAP, VIP, (K15, R16, L27)VIP(1-7)/GRF(8-27), (R16)ChSn) were shifted to the right by the %VPAC1% receptor %antagonist% (AcHis1, D-Phe2, Lys15, Leu17)VIP(3-7)/GRF(8-27), with a Ki of 3 +- 1 nM (n = 3). The presence of

%VPAC1% receptor mRNA was confirmed by RT-PCR. Preincubation with PACAP or PMA showed that %VPAC1% receptors underwent homologous and heterologous desensitization.

2/7/85 (Item 20 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

16464813 BIOSIS NO.: 200200058324
Vasoactive intestinal peptide has a direct positive inotropic effect on isolated human myocardial trabeculae
AUTHOR: Saetrum Opgaard Ole (Reprint); Knutsson Mikael; de Vries Rene; Tom Beril; Saxena Pramod R; Edvinsson Lars
AUTHOR ADDRESS: Department of Pharmacology, College of Medicine, University of California, 360 Med Surge II, Irvine, CA, 92697-4625, USA**USA
JOURNAL: Clinical Science (London) 101 (6): p637-643 December, 2001 2001
MEDIUM: print
ISSN: 0143-5221
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The aim of the present study was to assess the inotropic effects of vasoactive intestinal peptide (VIP) on isolated myocardial trabeculae from the right atrium and the left ventricle of human hearts. Furthermore, using reverse transcriptase-PCR, we wanted to determine the presence of mRNAs encoding the three cloned human VIP receptors, %VPAC1%, VPAC2 and PAC1. The trabeculae were paced at 1.0 Hz in tissue baths, and changes in isometric contractile force upon exposure to agonist were studied. VIP had a potent positive inotropic effect in some of the atrial and ventricular trabeculae tested. This effect was almost completely blocked by the VIP-receptor %antagonist% VIP-(6-28). mRNAs encoding the human %VPAC1%, VPAC2 and PAC1 receptors were detected in human myocardial trabeculae from both the right atrium and the left ventricle. In conclusion, VIP has a direct positive inotropic effect in both the atria and the ventricles of the human heart. The presence of mRNAs for the %VPAC1%, VPAC2 and PAC1 receptors suggest that VIP may mediate its effect via these receptors.

2/7/86 (Item 21 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

15824437 BIOSIS NO.: 200000542750
Creation of a selective %antagonist% and agonist of the rat %VPAC1% receptor using a combinatorial approach with vasoactive intestinal peptide 6-23 as template
AUTHOR: Tams Jeppe Wegener (Reprint); Jorgensen Rikke Malene; Holm Arne; Fahrenkrug Jan
AUTHOR ADDRESS: Department of Clinical Biochemistry, Bispebjerg Hospital, University of Copenhagen, DK-2400, Copenhagen NV: jwtams@biobase.dk, Denmark**Denmark
JOURNAL: Molecular Pharmacology 58 (5): p1035-1041 November, 2000 2000
MEDIUM: print
ISSN: 0026-895X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We have used combinatorial chemistry with amino acid mixtures (X) at positions 6 to 23 in vasoactive intestinal peptide (VIP) to optimize binding affinity and selectivity to the rat %VPAC1% receptor. The most efficient amino acid replacement was a substitution of alanine at position 18 to diphenylalanine (Dip), increasing the displacement efficiency of125I-VIP by 370-fold. The (Dip18)VIP(6-23) was subsequently used to find a second replacement, employing the same approach. Tyrosine at position 9 was selected and the resulting (Tyr9,Dip18)VIP(6-23) analog has a Ki value of 90 nM. This analog was unable to stimulate cAMP production at 10-6 M but was able to inhibit VIP-induced cAMP stimulation (Kb = 79 nM). The Ki values of (Tyr9,Dip18)VIP(6-23) using the rat VPAC2 and PAC1 receptors were 3,000 nM and >10,000 nM, respectively. Thus, (Tyr9,Dip18)VIP(6-23) is a selective %VPAC1% receptor %antagonist%. The C-terminally extended form, (Tyr9,Dip18)VIP(6-28), displays improved %antagonistic% properties having a Ki and Kb values of 18 nM and 16 nM, respectively. On the contrary, the fully extended form, (Tyr9,Dip18)VIP(1-28), was a potent agonist with improved binding affinity (Ki = 0.11 nM) and ability to stimulate cAMP (EC50 = 0.23 nM) compared with VIP (Ki = 1.7 nM, EC50 = 1.12 nM). Furthermore, the specificity of this agonist to the %VPAC1% receptor was high, the Ki values for the VPAC2 and PAC1 receptors were 53 nM and 3,100 nM, respectively. Seven other analogs with the (Tyr9,Dip18) replacement combined with previously published VIP modifications have been synthesized and described in this work.

2/7/87 (Item 22 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

15815105 BIOSIS NO.: 200000533418
Progesterone receptor activation mediates LH-induced type-I pituitary adenylate cyclase activating polypeptide receptor (PAC1) gene expression in rat granulosa cells
AUTHOR: Ko Chemyong (Reprint); Park-Sarge Ok-Kyong (Reprint)
AUTHOR ADDRESS: Department of Physiology, University of Kentucky, Lexington, KY, 40536, USA**USA
JOURNAL: Biochemical and Biophysical Research Communications 277 (1): p 270-279 October 14, 2000 2000
MEDIUM: print
ISSN: 0006-291X
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LANGUAGE: English

ABSTRACT: We have previously reported that the pituitary adenylate cyclase activating polypeptide (PACAP) gene is regulated in ovarian granulosa cells by the autocrine and/or paracrine interaction between progesterone and its nuclear receptor progesterone receptor (PR). To initiate studies on the functional significance of the progesterone-induced PACAP production in luteinizing granulosa cells, we sought to determine the expression and hormonal regulation of PACAP receptors in the rat ovary. The relative mRNA levels of three known PACAP receptor subtypes (PAC1, %VPAC1%, and VPAC2) were determined in ovaries of immature rats treated with gonadotropins, by semiquantitative reverse transcription-polymerase chain reaction (RT-PCR) assays. Results show that all PAC1, %VPAC1%, and VPAC2 transcripts are expressed at a detectable level in immature rat ovaries. Importantly, the ovarian level of PAC1, but not %VPAC1% or VPAC2, mRNA notably changes during gonadotropin challenges. Ovarian PAC1 mRNA expression decreases during the pregnant mare's serum gonadotropin (PMSG)-induced follicular phase but substantially increases during the human chorionic gonadotropin (hCG)-induced periovulatory period. Because the hCG-induced increase in ovarian PAC1 mRNA expression is attributable to the hormone-induced PAC1 mRNA expression in granulosa cells of the preovulatory follicles, we next examined whether hCG regulates PAC1 mRNA expression by directly acting on granulosa cells. When granulosa cells isolated from PMSG (40 h)-primed immature rats were challenged with hCG (or forskolin), PAC1, but not %VPAC1% or VPAC2, mRNA expression significantly increased within 6 h. Because the LH-induced PAC1 mRNA expression (6 h) proceeds PR activation (3 h) in granulosa cells as the LH-induced PACAP mRNA expression (6 h) does, we further determined the cause-effect relationship among LH, PR activation and PAC1 receptor gene expression, by examining the effect of PR %antagonist%, ZK98299, on the ability of LH to increase PAC1 mRNA levels in luteinizing granulosa cells. Results show that ZK98299 inhibited the stimulatory effect of hCG (or forskolin) on PAC1 mRNA expression, at the level of all known splice variants of PAC1 mRNA in granulosa cells. In summary, our results demonstrating that PR activation is critical for the LH-induced PAC1 gene expression in luteinizing granulosa cells suggest that PR activation

regulates the finely tuned expression of the PACAP/PACAP receptor genes in luteinizing granulosa cells and thus dictates the timing of the autocrine and/or paracrine function of PACAP in preovulatory follicles.

2/7/88 (Item 23 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

15542591 BIOSIS NO.: 200000260904
Vasoactive intestinal peptide and pituitary adenylyl cyclase-activating polypeptide inhibit tumor necrosis factor-alpha production in injured spinal cord and in activated microglia via a cAMP-dependent pathway
AUTHOR: Kim Woong-Ki; Kan Yanqing; Ganea Doina; Hart Ronald P; Gozes Illana ; Jonakait G Miller (Reprint)
AUTHOR ADDRESS: Department of Biological Sciences, Rutgers University, 101 Warren Street, Newark, NJ, 07102, USA**USA
JOURNAL: Journal of Neuroscience 20 (10): p3622-3630 May 15, 2000 2000
MEDIUM: print
ISSN: 0270-6474
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Tumor necrosis factor-alpha (TNF-alpha) production accompanies CNS insults of all kinds. Because the neuropeptide vasoactive intestinal peptide (VIP) and the structurally related peptide pituitary adenylyl cyclase-activating polypeptide (PACAP) have potent anti-inflammatory effects in the periphery, we investigated whether these effects extend to the CNS. TNF-alpha mRNA was induced within 2 hr after rat spinal cord transection, and its upregulation was suppressed by a synthetic VIP receptor agonist. Cultured rat microglia were used to examine the mechanisms underlying this inhibition because microglia are the likely source of TNF-alpha in injured CNS. In culture, increases in TNF-alpha mRNA resulting from lipopolysaccharide (LPS) stimulation were reduced significantly by 10-7 M VIP and completely eliminated by PACAP at the same concentration. TNF-alpha protein levels were reduced 90% by VIP or PACAP at 10-7 M. An %antagonist% of %VPAC1% receptors blocked the action of VIP and PACAP, and a PAC1 %antagonist% blocked the action of PACAP. A direct demonstration of VIP binding on microglia and the existence of mRNAs for %VPAC1% and PAC1 (but not VPAC2) receptors argue for a receptor-mediated effect. The action of VIP is cAMP-mediated because (1) activation of cAMP by forskolin mimics the action; (2) PKA inhibition by H89 reverses the neuropeptide-induced inhibition; and (3) the lipophilic neuropeptide mimic, stearyl-norleucine17 VIP (SNV), which does not use a cAMP-mediated pathway, fails to duplicate the inhibition. We conclude that VIP and PACAP inhibit the production of TNF-alpha from activated microglia by a cAMP-dependent pathway.

2/7/89 (Item 24 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

15419012 BIOSIS NO.: 200000137325
%Antagonistic% actions of analogs related to growth hormone-releasing hormone (GHRH) on receptors for GHRH and vasoactive intestinal peptide on rat pituitary and pineal cells in vitro
AUTHOR: Rekasi Zoltan; Varga Jozsef L; Schally Andrew V (Reprint); Halmos Gabor; Groot Kate; Czompoly Tamas
AUTHOR ADDRESS: Veterans Affairs Medical Center, 1601 Perdido Street, New Orleans, LA, 70112-1262, USA**USA
JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 97 (3): p1218-1223 Feb. 1, 2000 2000
MEDIUM: print
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Peptide analogs of growth hormone-releasing hormone (GHRH) can potentially interact with vasoactive intestinal peptide (VIP) receptors (%VPAC1%-R and VPAC2-R) because of the structural similarities of these two hormones and their receptors. We synthesized four new analogs related to GHRH (JV-1-50, JV-1-51, JV-1-52, and JV-1-53) with decreased GHRH %antagonistic% activity and increased VIP %antagonistic% potency. To characterize various peptide analogs for their %antagonistic% activity on receptors for GHRH and VIP, we developed assay systems based on superfusion of rat pituitary and pineal cells. Receptor-binding affinities of peptides to the membranes of these cells were also evaluated by radioligand competition assays. Previously reported GHRH %antagonists% JV-1-36, JV-1-38, and JV-1-42 proved to be selective for GHRH receptors, because they did not influence VIP-stimulated VPAC2 receptor-dependent prolactin release from pituitary cells or %VPAC1% receptor-dependent cAMP efflux from pinealocytes but strongly inhibited GHRH-stimulated growth hormone (GH) release. Analogs JV-1-50, JV-1-51, and JV-1-52 showed various degrees of %VPAC1%-R and VPAC2-R %antagonistic% potency, although also preserving a substantial GHRH %antagonistic% effect. Analog JV-1-53 proved to be a highly potent %VPAC1% and VPAC2 receptor %antagonist%, devoid of inhibitory effects on GHRH-evoked GH release. The %antagonistic% activity of these peptide analogs on processes mediated by receptors for GHRH and VIP was consistent with the binding affinity. The analogs with %antagonistic% effects on different types of receptors expressed on tumor cells could be utilized for the development of new approaches to treatment of various human cancers.

2/7/90 (Item 25 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

15384491 BIOSIS NO.: 200000102804
Different vasoactive intestinal polypeptide receptor domains are involved in the selective recognition of two VPAC2-selective ligands
AUTHOR: Juarranz Maria G; Van Rampelbergh Jean; Gourlet Philippe; De Neef Philippe; Cnudde Johnny; Robberecht Patrick; Waelbroeck Magali (Reprint)
AUTHOR ADDRESS: Department of Biochemistry and Nutrition, Faculty of Medicine, Universite Libre de Bruxelles, 808 Route de Lennik, Bat. G/E, 1070, Brussels, Belgium**Belgium
JOURNAL: Molecular Pharmacology 56 (6): p1280-1287 Dec., 1999 1999
MEDIUM: print
ISSN: 0026-895X
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A vasoactive intestinal polypeptide (VIP) analog, acylated on the amino-terminal histidine by hexanoic acid (C6-VIP), behaved as a VPAC2 preferring agonist in binding and functional studies on human VIP receptors, and radioiodinated C6-VIP was a suitable ligand for binding studies on wild-type and chimeric receptors. We evaluated the properties of C6-VIP, its analog AcHis1-VIP, and the VPAC2-selective agonist Ro 25-1553 on the wild-type %VPAC1% and VPAC2 receptors and on the chimeric receptors exchanging the different domains between both receptors. VIP had a normal affinity and efficacy on the chimeras starting with the amino-terminal VPAC2 receptor sequence. The binding and functional profile of these chimeric receptors suggested that the high affinity of Ro 25-1553 for VPAC2 receptors is supported by the amino-terminal extracellular domain, whereas the ability to prefer C6-VIP over VIP is supported by the VPAC2 fifth transmembrane (TM5)-EC3 receptor domain. These results further support the hypothesis that the central and carboxyl-terminal regions of the peptide (modified in RO 25-1553) recognize the extracellular amino-terminal region domain, whereas the amino-terminal VIP amino acids bind to the TM receptor core. VIP had a reduced affinity and efficacy on the N-%VPAC1%/VPAC2 and on the NfwdarwEC2-%VPAC1%/VPAC2 chimeric receptors. C6-VIP behaved as a high-affinity agonist on these constructions. The %antagonists% (AcHis1,D-Phe2,Lys15,Arg16,Leu27)VIP(3-7)/GRF(8-27) and VIP(5-27) had comparable affinities for the wild-type receptors and for the two latter

chimeras, supporting the hypothesis that these chimeras were properly folded but unable to reach the high-agonist-affinity, active receptor conformation in response to VIP binding.

2/7/91 (Item 26 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

15209184 BIOSIS NO.: 199900468844
Comparison of the effects of VIP and PACAP on steroid secretion of dispersed rat adrenocortical cells
AUTHOR: Nowak Krzysztof W; Neri Giuliano; Nussdorfer Gastone G (Reprint); Malendowicz Ludwik K
AUTHOR ADDRESS: Department of Human Anatomy and Physiology, Section of Anatomy, University of Padua, Padua, Italy**Italy
JOURNAL: Biomedical Research (Tokyo) 20 (3): p127-132 June, 1999 1999
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The effects of vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP)-38 or -27, and their receptor %antagonists% (VIP-A, P38-A and P27-A) have been investigated on aldosterone and corticosterone secretion in dispersed rat zona glomerulosa (ZG) and zona fasciculata-reticularis (ZF/R) cells. VIP and PACAP-38 enhanced both aldosterone and corticosterone production, VIP being much more effective than PACAP-38. PACAP-27 elicited only a moderate increase in corticosterone production. The ACTH receptor %antagonist% corticotropin-inhibiting peptide and the beta-adrenoceptor %antagonist% l-alprenolol did not affect hormonal response to the maximal effective concentration (10-6 M) of VIP and PACAPs. VIP-A, which is an %antagonist% of %VPAC1% receptor subtype, counteracted only corticosterone response to PACAP-38. P38-A, which is an %antagonist% of PAC1 receptor and VPAC2 receptor subtypes, hampered aldosterone response to VIP and PACAP-38, and corticosterone response to VIP and PACAP-27. P27-A, whose receptor selectivity is not known. VIP-A potentiated corticosterone response to VIP, and aldosterone response to PACAP-38. These findings led us to conclude: (i) VIP and PACAPs stimulate secretion of rat adrenocortical cells, through the activation of specific receptors, being their effectiveness VIP > PACAP-38 MUGT PACAP-27; and (ii) aldosterone response of ZG cells to VIP and PACAPs is probably mediated by PAC1 and VPAC2 receptors, while corticosterone response of ZF/R cells involves also the %VPAC1% receptor subtype.

2/7/92 (Item 27 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

15192551 BIOSIS NO.: 199900452211
Vasoactive intestinal polypeptide receptor %VPAC1% subtype is predominant in rat prostate membranes
AUTHOR: Juarranz Maria G (Reprint); De Neef Philippe; Robberecht Patrick
AUTHOR ADDRESS: Laboratoire de Chimie Biologique et de la Nutrition, Faculte de Medecine de l'Universite Libre de Bruxelles, 808 Route de Lennik, Bat. G/E, B-1070, Brussels, Belgium**Belgium
JOURNAL: Prostate 41 (1): p1-6 Sept. 15, 1999 1999
MEDIUM: print
ISSN: 0270-4137
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: BACKGROUND. The 28-amino-acid neuropeptide vasoactive intestinal peptide (VIP) might play an important role in the physiology of the prostate, since it stimulates glandular secretion, inhibits muscle contraction, stimulates proliferation of epithelial cells, and increases the secretion of prostate-specific antigen (PSA). This neuropeptide may act through interaction with two types of high-affinity receptors, named %VPAC1% and VPAC2 receptors. Recently, selective agonists and %antagonists% for each receptor subtype were synthesized. We used them to identify the VIP receptor subclass expressed in rat prostatic tissue. METHODS. We tested the capacity of selective labeled and unlabeled agonists and %antagonists% of %VPAC1% and VPAC2 receptors to bind to rat prostatic membranes and to stimulate or prevent the stimulation of adenylate cyclase activity. RESULTS. The following selective peptides were used: %VPAC1% agonist ((K15, R16, L27) VIP (1-7)/GRF (8-27)); %VPAC1% %antagonist% (PG 97-269); and VPAC2 agonist (RO 25-1553). The IC50 values of (125I)-VIP binding inhibition for the different peptides in rat prostatic membranes were: VIP (1.7 nM) < %VPAC1% agonist (20 nM) < %VPAC1% %antagonist% (40 nM) < VPAC2 agonist (329 nM). The EC50 values of adenylate cyclase stimulation were similar to the IC50 values for each peptide, and the Ki values for the %VPAC1% %antagonist%, inhibiting the adenylate cyclase activity stimulated by VIP and the %VPAC1% agonist, were 22 and 35 nM,respectively. Comparison of binding of (125I)-VIP and of (125I)-RO 25-1553 indicates the presence of 80% of %VPAC1% and 20% VPAC2 receptors. CONCLUSIONS. In rat prostate membranes, %VPAC1% receptors are largely predominant. Binding studies were compatible with a ratio of 80/20 of %VPAC1%/VPAC2 receptors, whereas functionally only %VPAC1% receptors were detected.

2/7/93 (Item 28 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

15124061 BIOSIS NO.: 199900383721
Expression, pharmacological, and functional evidence for PACAP/VIP receptors in human lung
AUTHOR: Busto Rebeca; Carrero Isabel; Guijarro Luis G; Solano Rosa M; Zapatero Jose; Noguerales Fernando; Prieto Juan C (Reprint)
AUTHOR ADDRESS: Unidad de Neuroendocrinologia Molecular, Departamento de Bioquimica y Biologia Molecular, Universidad de Alcala, E-28871, Alcala de Henares, Spain**Spain
JOURNAL: American Journal of Physiology 277 (1 PART 1): pL42-L48 July, 1999 1999
MEDIUM: print
ISSN: 0002-9513
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Pituitary adenylate cyclase-activating peptide (PACAP) type 1 (PAC1) and common PACAP/vasoactive intestinal peptide (VIP) type 1 and 2 (%VPAC1% and VPAC2, respectively) receptors were detected in the human lung by RT-PCR. The proteins were identified by immunoblotting at 72, 67, and 68 kDa, respectively. One class of PACAP receptors was defined from 125I-labeled PACAP-27 binding experiments (dissociation constant = 5.2 nM; maximum binding capacity = 5.2 pmol/mg protein) with a specificity: PACAP-27 apprxeq VIP > helodermin apprxeq peptide histidine-methionine (PHM) mchgt secretin. Two classes of VIP receptors were established with 125I-VIP (dissociation constants of 5.4 and 197 nM) with a specificity: VIP apprxeq helodermin apprxeq PACAP-27 mchgt PHM mchgt secretin. PACAP-27 and VIP were equipotent on adenylyl cyclase stimulation (EC50 = 1.6 nM), whereas other peptides showed lower potency (helodermin > PHM mchgt secretin). PACAP/VIP %antagonists% supported that PACAP-27 acts in the human lung through either specific receptors or common PACAP/VIP receptors. The present results are the first demonstration of the presence of PAC1 receptors and extend our knowledge of common PACAP/VIP receptors in the human lung.

2/7/94 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

14580763 Genuine Article#: 987KI Number of References: 51

Title: Photoaffinity cross-linking of the corticotropin-releasing factor receptor type 1 with photoreactive urocortin analogues
Author(s): Kraetke O (REPRINT) ; Holeran B; Berger H; Escher E; Bienert M; Beyermann M
Corporate Source: FMP,Inst Mol Pharmacol, Dept Peptide Chem,D-13125 Berlin//Germany/ (REPRINT); FMP,Inst Mol Pharmacol, Dept Peptide Chem,D-13125 Berlin//Germany/; Univ Sherbrooke,Fac Med, IPS, Dept Pharmacol,Sherbrooke/PQ J1H 5N4/Canada/(kraetke@fmp-berlin.de)
Journal: BIOCHEMISTRY, 2005, V44, N47 (NOV 29), P15569-15577
ISSN: 0006-2960 Publication date: 20051129
Publisher: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036 USA
Language: English Document Type: ARTICLE
Abstract: Interaction of natural peptide ligands with class 2 GPCRs, which are targets of biologically important hormones such as glucagon, secretin, and corticotropin-releasing factor (CRF), occurs with a common orientation, in that the ligand C-terminus binds to the extracellular receptor N-terminus, whereas the ligand N-terminus binds to the receptor juxtamembrane domain. N-Terminal truncation, by eight amino acids in the case of CRF, leads to %antagonists%, suggesting those residues constitute the receptor activating sequence. Here, we identified by photoaffinity cross-linking using p-benzoyl-L-phenylaianine (Bpa) analogues of urocortin (Ucn) the most affine CRF receptor agonist, interaction domains of CRF1 receptor with Bpa residues at exclusive positions. Specific cleavage patterns of the corresponding ligand-receptor complexes, obtained using several cleavage methods in combination with SDS-PAGE for fragment size determination, showed that a Bpa group located N-terminally or in position 12 binds at the second and such in position 17 or 22 at the first extracellular receptor loop. Our results indicate that the very N-terminal ligand residues (1-11), which are responsible for receptor activation, are oriented to the juxtamembrane domain by interaction of amino acid residues 12, 17, and 22. Our findings contradict a recently proposed interaction model derived from ligand interaction with a soluble receptor N-terminus, indicating that conclusions drawn from such a reduced system may be of limited value to understand the interaction with the full-length receptor.

2/7/95 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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13410034 Genuine Article#: 876TM Number of References: 123
Title: Potential clinical applications of vasoactive intestinal peptide: a selected update
Author(s): Gozes A (REPRINT) ; Furman S
Corporate Source: Tel Aviv Univ,Sackler Fac Med, Dept Clin Biochem,IL-69978 Tel Aviv//Israel/ (REPRINT); Tel Aviv Univ,Sackler Fac Med, Dept Clin Biochem,IL-69978 Tel Aviv//Israel/(igozes@post.tau.ac.il)
Journal: BEST PRACTICE & RESEARCH CLINICAL ENDOCRINOLOGY & METABOLISM, 2004, V18, N4 (DEC), P623-640
ISSN: 1521-690X Publication date: 20041200
Publisher: BAILLIERE TINDALL, 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND
Language: English Document Type: REVIEW
Abstract: Neuropeptides are expressed in neurons innervating endocrine cells or in endocrine cells and cancer cells, and are released on site to act as hormones and growth factors. Vasoactive intestinal peptide (VIP) was first discovered in the early 1970s and has since become the area of research for many laboratories. VIP has a neuroendocrine role as it is intimately involved with the synthesis, secretion and action of other neuroendocrine hormones as well as cytokines and chemokines. Major outcomes of VIP downregulation encompass developmental and behavioral dysfunctions, including impaired diurnal rhythms. Overexpression of VIP has been associated with diarrhea and cancer, and overexpression of VIP receptors is associated with cancerous growth. This short review outlines some of the recent progress made in VIP research.

2/7/96 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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10994200 Genuine Article#: 594DZ Number of References: 45
Title: Phospholipids modulate the biophysical properties and vasoactivity of PACAP-(1-38)
Author(s): Tsueshita T; Gandhi S; Onyuksel H; Rubinstein I (REPRINT)
Corporate Source: Univ Illinois,Dept Biopharmaceut Sci,M-C 865,833 S Wood St/Chicago//IL/60612 (REPRINT); Univ Illinois,Dept Biopharmaceut Sci,Chicago//IL/60612; Univ Illinois,Dept Bioengn,Chicago//IL/60612; Univ Illinois,Dept Med,Chicago//IL/60612; Chicago Vet Affairs Hlth Care Syst,W Side Div,Chicago//IL/60612
Journal: JOURNAL OF APPLIED PHYSIOLOGY, 2002, V93, N4 (OCT), P1377-1383
ISSN: 8750-7587 Publication date: 20021000
Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA
Language: English Document Type: ARTICLE
Abstract: The purpose of this study was to elucidate the interactions between pituitary adenylate cyclase-activating peptide (PACAP)-(1-38) and phospholipids in vitro and to determine whether these phenomena modulate, in part, the vasorelaxant effects of the peptide in the intact peripheral microcirculation. We found that the critical micellar concentration of PACAP-(1-38) was 0.4-0.9 muM. PACAP-(1-38) significantly increased the surface tension of a dipalmitoylphosphatidylcholine monolayer and underwent conformational transition from predominantly random coil in saline to alpha-helix in the presence of distearoyl-phosphatidylethanolamine-polyethylene glycol (molecular mass of 2,000 Da) sterically stabilized phospholipid micelles (SSM) ($P < 0.05$). Using intravital microscopy, we found that aqueous PACAP-(1-38) evoked significant concentration-dependent vasodilation in the intact hamster cheek pouch that was significantly potentiated when PACAP-(1-38) was associated with SSM ($P < 0.05$). The vasorelaxant effects of aqueous PACAP-(1-38) were mediated predominantly by PACAP type 1 (PAC(1)) receptors, whereas those of PACAP-(1-38) in SSM predominantly by PACAP/vasoactive intestinal peptide type 1 and 2 (%VPAC1%/VPAC2) receptors. Collectively, these data indicate that PACAP-(1-38) self-associates and interacts avidly with phospholipids in vitro and that these phenomena amplify peptide vasoactivity in the intact peripheral microcirculation.

2/7/97 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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07971153 Genuine Article#: 230UY Number of References: 12
Title: Evidence for multiple rat VPAC(1) receptor states with different affinities for agonists
Author(s): Busto R; Juarranz MG; DeMaria S; Robberecht P (REPRINT) ; Waelbroeck M
Corporate Source: FREE UNIV BRUSSELS,FAC MED, DEPT BIOCHEM & NUTR, CP 611, 808 ROUTE LENNIK/B-1070 BRUSSELS//BELGIUM/ (REPRINT); FREE UNIV BRUSSELS,FAC MED, DEPT BIOCHEM & NUTR/B-1070 BRUSSELS//BELGIUM/
Journal: CELLULAR SIGNALLING, 1999, V11, N9 (SEP), P691-696
ISSN: 0898-6568 Publication date: 19990900
Publisher: ELSEVIER SCIENCE INC, 655 AVENUE OF THE AMERICAS, NEW YORK, NY 10010
Language: English Document Type: ARTICLE
Abstract: We compare the binding properties of [I-125-VIP] and [I-125]-Ro 25 1553 to VPAC(1) receptors, expressed in stably transfected CHO cells. [I-125]-VIP labelled two %VPAC1% receptor states, while [I-125]-Ro 25 1553 labelled selectively a limited number of high-affinity receptors. This high-affinity state probably corresponds to an agonist-receptor-G, ternary complex as its properties (guanyl nucleotides, EC50 values and maximal effect) were affected by cholera toxin pre-treatment. Both high- and low-affinity receptors participated in the adenylate cyclase activation. This suggested that agonists activate not only low-affinity uncoupled receptors by facilitating the ternary complex formation, but also activated the high-affinity ternary complex by accelerating the GTP binding to emptied, receptor-bound G

proteins. (C) 1999 Elsevier Science Inc.

2/7/98 (Item 1 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE
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02400120 2003183819
VIP and PACAP are autocrine factors that protect the androgen-independent prostate cancer cell line PC-3 from apoptosis induced by serum withdrawal
Gutierrez-Can(tilde)as I.; Rodriguez-Henche N.; Bolan(tilde)os O.; Carmena M.J.; Prieto J.C.; Juarranz M.G.
ADDRESS: J.C. Prieto, Biochemistry and Molecular Biology, University of Alcala, Campus Universitario, Alcala de Henares, Madrid 28871, Spain
EMAIL: juancarlos.prieto@uah.es
Journal: British Journal of Pharmacology, 139/5 (1050-1058), 2003, United Kingdom
CODEN: BJPCB
ISSN: 0007-1188
DOCUMENT TYPE: Article
LANGUAGES: English SUMMARY LANGUAGES: English
NO. OF REFERENCES: 35

1. In the present study, we describe the expression of the neuropeptides vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) as well as their receptors in PC-3 cells, a human prostate cancer cell line. In addition, we have investigated their role in apoptosis induced by serum starvation. 2. By RT-PCR and immunocytochemistry assays, we have demonstrated the production of VIP and PACAP in PC-3 cells. 3. We have demonstrated by RT-PCR and binding assays the expression of common PACAP/VIP (VPACSUB1 and VPACSUB2) receptors, but not PACAP-specific (PACSUB1) receptors. The pharmacological profile of [SUP125I]-VIP binding assays was as follows: VPACSUB1 %antagonist% = VPACSUB1 agonist > VIP > V-PACSUB2 agonist (ICSUB50 = 1.2, 1.5, 2.3 and 30 nM, respectively). In addition, both receptor subtypes are functional since VIP, PACAP-27 or %VPAC1% and VPAC: agonists all increased the intracellular levels of cAMP. 4. The expression of both peptides and their receptors is similar in serum-cultured and serum-deprived PC-3 cells. The treatment of serum-deprived PC-3 cells with exogenous VIP or PACAP-27 increases cell number and viability in a dose-dependent manner, as demonstrated by cellular counting and MTT assays. The increased cell survival is exerted through the VPACSUB1 receptor, since a VPACSUB1, but not VPACSUB2, receptor agonist, mimics the effects and a VPACSUB1 receptor %antagonist% blocks it. Moreover, VIP and PACAP-27 inhibit genomic DNA fragmentation in PC-3 cells triggered by serum starvation, and increase the immunoreactivity of the antiapoptotic protein bcl-2. 5. Our results suggest that VIP and PACAP are autocrine/paracrine factors that protect PC-3 cells from apoptosis through VPACSUB1 receptors.

2/7/99 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
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13219655 EMBASE No: 2005264953
VIP enhances synaptic transmission to hippocampal CA1 pyramidal cells through activation of both VPACSUB1 and VPACSUB2 receptors
Cunha-Reis D.; Ribeiro J.A.; Sebastia(tilde)o A.M.
D. Cunha-Reis, Institute of Pharmacology and Neurosciences, Faculty of Medicine and Institute of Molecular Medicine, University of Lisbon, Av. Prof. Egas Moniz, 1649-028 Lisbon Portugal
AUTHOR EMAIL: diana-reis@fm.ul.pt
Brain Research (BRAIN RES.) (Netherlands) 05 JUL 2005, 1049/1 (52-60)
CODEN: BRREA ISSN: 0006-8993
PUBLISHER ITEM IDENTIFIER: S0006899305006852
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 31

We previously described that vasoactive intestinal peptide (VIP) increases synaptic transmission to hippocampal CA1 pyramidal cells at concentrations known to activate VIP-selective receptors (VPACSUB1 and VPACSUB2) but not the PACAP-selective PACSUB1 receptor. We now investigated the involvement of VPACSUB1 and VPACSUB2 receptors in the effects elicited by VIP as well as the transduction pathways activated by VIP to cause enhancement of synaptic transmission. Blockade of either VPACSUB1 or VPACSUB2 receptors with PG 97-269 (100 nM) or PG 99-465 (100 nM) inhibited VIP-induced enhancement of synaptic transmission. Selective activation of VPACSUB1 receptors with [KSUP15, RSUP16, L SUP27] VIP(1-7)/GRF(8-27) (10 nM) or of VPACSUB2 receptors with RO 25-1553 (10 nM) increased synaptic transmission to CA1 pyramidal cells, and this increase was larger when both agonists were applied together. Inhibition of either PKA with H-89 (1 muM) or PKC with GF109203X (1 muM) attenuated the effect of VIP (1 nM). GF109203X (1 muM) abolished the effect of the VPAC SUB1 agonist [KSUP15, RSUP16, LSUP27] VIP(1-7)/GRF(8-27) (10 nM) on hippocampal synaptic transmission but that effect was not changed by H-89 (1 muM). The effect of RO 25-1553 (100 nM) obtained in the presence of both the PACSUB1 and VPACSUB1 %antagonists%, M65 (30 nM) and PG 97-269 (100 nM), was strongly inhibited by H-89 (1 muM) but not GF109203X (1 muM). It is concluded that VIP enhances synaptic transmission to CA1 pyramidal cell dendrites through VPACSUB1 and VPACSUB2 receptor activation. VPACSUB1-mediated actions are dependent on PKC activity, and VPACSUB2-mediated actions are responsible for the PKA-dependent actions of VIP on CA1 hippocampal transmission.

2/7/100 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE
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12856260 EMBASE No: 2004449289
Ac HisSUP1 [D-PheSUP2, KSUP15, RSUP16, LSUP27] VIP (3-7)/GRF (8-27) - A VPACSUB1 receptor %antagonist% - Is an inverse agonist on two constitutively active truncated VPACSUB1 receptors
Vertongen P.; Langlet C.; Langer I.; Gaspard N.; Robberecht P.
P. Vertongen, Dept. of Biochemistry and Nutrition, School of Medicine, Univ. Libre Bruxelles, Bat G/E, C., Bruxelles Belgium
AUTHOR EMAIL: pvertong@ulb.ac.be
Peptides (PEPTIDES) (United States) 2004, 25/11 (1943-1949)
CODEN: PEPTD ISSN: 0196-9781
PUBLISHER ITEM IDENTIFIER: S0196978104002530
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 26

C-terminally truncated human VPACSUB1 receptors were constructed and stably transfected in Chinese hamster ovary (CHO) cells. Selected clones expressing comparable receptor densities were studied for ligand's binding properties, basal and stimulated adenylate cyclase activity. The wild-type (1-457) receptor served as reference. The binding properties of all the constructions were preserved. As judged by the intrinsic activity of the partial agonist QSUP3-VIP, the shortest receptors have a moderate impairment of the coupling efficacy to GSUBalphas protein. Cells expressing the VPACSUB1 (1-436) and (1-441) truncated receptors had a two- to three-fold higher basal adenylate cyclase activity than those expressing the wild-type or the VPACSUB1 (1-444), (1-433), (1-429), (1-421) and (1-398) receptor. The stimulatory effect of VIP and other agonist was preserved. This suggested that VPACSUB1 (1-436) and (1-441) receptors had a constitutive activity. The selective VPACSUB1 receptor %antagonist% Ac HisSUP1 [D-PheSUP2, KSUP15, RSUP16, LSUP27] VIP (3-7)/GRF (8-27) reduced by 60% the basal activity with an ECSUB50 value of 3 nM comparable to its ICSUB50 value for binding. This agonist behaved thus like an inverse agonist on the constitutively active VPAC SUB1 receptors generated by C-terminal truncation and expressed in CHO cells. (c) 2004 Elsevier Inc. All rights reserved.

2/7/101 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE
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11938818 EMBASE No: 2003051308
Lysine 195 and aspartate 196 in the first extracellular loop of the VPACSUB1 receptor are essential for high affinity binding of agonists but not of %antagonists%
Langer I.; Vertongen P.; Perret J.; Waelbroeck M.; Robberecht P.
I. Langer, Dept. of Biol. Chem. and Nutrition, Faculty of Medicine, Universite Libre de Bruxelles, 808 Route de Lennik, B-1070 Brussels Belgium
AUTHOR EMAIL: ilanger@ulb.ac.be
Neuropharmacology (NEUROPHARMACOLOGY) (United Kingdom) 2003, 44/1 (125-131)
CODEN: NEPHB ISSN: 0028-3908
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 22

The role in ligand recognition and receptor activation of two adjacent charged residues (lysine 195 and aspartate 196) in the first extracellular loop of the human VPACSUB1 receptor was investigated in stably transfected CHO cells expressing the wild type or point mutated receptors. Replacement of lysine 195 by glutamine or of aspartate 196 by asparagine reduced the agonists' ability to stimulate adenylate cyclase activity; VIP behaved like a partial agonist and a partial agonist behaved as an %antagonist%. The receptor's capacity to recognize agonists was reduced but %antagonists%' affinity was unaffected. Both results suggesting that the two charged residues are essential for VPACSUB1 receptor activation. On the other hand, the double mutant was less severely affected than single mutants suggesting that hydrogen bonds may partially compensate the loss of charged residues. But the inversion of the residues affected receptor recognition and activation more markedly suggesting that the two charged residues do not interact directly. (c) 2002 Elsevier Science Ltd. All rights reserved.

2/7/102 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE
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11792760 EMBASE No: 2002364622
PAC1 receptor-mediated relaxation of longitudinal muscle of the mouse proximal colon
Mukai K.; Satoh Y.; Fujita A.; Takeuchi T.; Shintani N.; Hashimoto H.; Baba A.; Hata F.
T. Takeuchi, Dept. of Veterinary Pharmacology, Grad. Sch. of Agric. and Life Sci., Osaka Prefecture University, Sakai 599-8531 Japan
AUTHOR EMAIL: takeuchi@vet.osakafu-u.ac.jp
Japanese Journal of Pharmacology (JPN. J. PHARMACOL.) (Japan) 01 SEP 2002, 90/1 (97-100)
CODEN: JJPAA ISSN: 0021-5198
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 16

Since pituitary adenylate cyclase-activating polypeptide (PACAP) was shown to partially mediate nonadrenergic, noncholinergic (NANC) relaxation of longitudinal muscle of the proximal colon of ICR mice, we further studied the receptor subtype activated by PACAP by using a mutant mouse whose PAC1 receptors are markedly reduced. In wild-type mice, the PACAP-mediated component of NANC relaxation was 33%, but it was absent in the mutant mice. The potency of exogenous PACAP in inducing relaxation in the mutant mice was one hundredth of that in wild-type mice. %VPAC1% and VPAC2 receptors were not suggested to have any role in the relaxation. These results suggest that PACAP mediates NANC relaxation of longitudinal muscle of mouse proximal colon via PAC1 receptors.

2/7/103 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE
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11628634 EMBASE No: 2002201350
Effect of vasoactive intestinal polypeptide on growth regulation in human pancreatic carcinoma
Gong L.-B.; Wang M.-C.; Cheng C.; Yan J.-C.; Jiang R.-L.
L.-B. Gong, Department of Gastroenterlogy, Second Clinical Hospital, Shenyang Medical College, Shenyang 110002, Laoning Province China
World Chinese Journal of Digestology (WORLD CHIN. J. DIG.) (China) 2002, 10/5 (562-565)
CODEN: SHXZF ISSN: 1009-3079
DOCUMENT TYPE: Journal ; Article
LANGUAGE: CHINESE SUMMARY LANGUAGE: ENGLISH; CHINESE
NUMBER OF REFERENCES: 30

AIM: To explore the effect and mechanisms of vasoactive intestinal polypeptide (VIP) on the growth of human pancreatic carcinoma cell lines AsPC-1 and PANC-1. METHODS: After serum-free culture for 24 hours and treatment with VIP (10SUP-11 mol/L (similar) 10SUP-5 mol/L), AsPC-1 and PANC-1 cell growth were quantified by MTT assay. %VPAC1% mRNA was then analyzed with RT-PCR. The mutation of K-ras gene at codon 12 was detected with DNA sequencing and the phosphorylation of mitogen-activated protein kinase (MAPK) was evaluated with Western blot. RESULTS: VIP of 10SUP-9, 10SUP-8, 10SUP-7, 10SUP-6 and 10SUP-5 mol/L significantly promoted the growth of AsPC-1 cells and maximum activated effect was exerted by 10SUP-8. The proliferation of AsPC-1 cells could be inhibited by (D-P-cl-Phe6-Len17) VIP, which was the %antagonist% of VIP receptor. Western blot analysis showed that the phosphorylation of MAPK (ERK) was upgrade, whereas the results of DNA sequencing showed that there was no point mutation at codon 12 in K-ras gene. CONCLUSION: VIP can significantly enhance the proliferation of human pancreatic carcinoma cell line AsPC-1. The mechanism is probably associated with the activating of MAPK signaling pathway but does not involve the mutatin of K-ras gene.

2/7/104 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE
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11281609 EMBASE No: 2001296308
Proline residue 280 in the second extracellular loop (EC2) of the VPACSUB2 receptor is essential for the receptor structure
Vertongen P.; Solano R.M.; Juarranz M.G.; Perret J.; Waelbroeck M.; Robberecht P.
P. Robberecht, Department of Biochemistry, School of Medicine, Universite Libre de Bruxelles, 808 route de Lennik, B-1070 Bruxelles Belgium
AUTHOR EMAIL: probbe@ulb.ac.be
Peptides (PEPTIDES) (United States) 2001, 22/9 (1363-1370)
CODEN: PEPTD ISSN: 0196-9781
PUBLISHER ITEM IDENTIFIER: S0196978101004764
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 32

Inspection of the amino acid sequence of the human VPACSUB1 and the VPACSUB2 receptors after alignment of the conserved residues indicates that the second extracellular loop (EC2) is one amino acid shorter in the VPACSUB1 receptor due to the lack of a proline residue in position 294. We hypothesized that this could be of importance for receptor structure and/or for ligand recognition. Insertion by directed mutagenesis of a proline in that position (<Pro>294 VPACSUB1) had little consequence on the binding of several agonists but reduced the affinity for the VPACSUB1 %antagonist%. Coupling of the <Pro>294 VPACSUB1 receptor to adenylate cyclase was improved, as demonstrated by an increased affinity for VIP and other agonists, and by a shift of the VPACSUB1 %antagonist% to partial agonist behavior. Deletion of the proline 280 (DELTAPro280 VPACSUB2) in the VPACSUB2 receptor markedly reduced the apparent affinity for all the agonists tested. Replacement of the proline by a glycine residue had a smaller effect on the ligands affinities. The proline residue in the VPACSUB2 receptor EC2 is thus essential for the receptor structure, and the EC2 domain is involved in ligand recognition and receptor functionality.
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2/7/105 (Item 1 from file: 135)
DIALOG(R)File 135:NewsRx Weekly Reports

0000444851 (THIS IS THE FULLTEXT)
New University of South Florida, U.S., study results described
Pharma Business Week, February 12, 2007, p.1522

DOCUMENT TYPE: Expanded Reporting LANGUAGE: English
RECORD TYPE: FULLTEXT
AUDIENCE: Professional
WORD COUNT: 1128

TEXT: New University of South Florida, U.S., study results described.

This trend article about University of South Florida, U.S., is an immediate alert from NewsRx to identify developing directions of research.

Study 1: Fresh data on proteomics are presented in the report "Mechanisms of vasoactive intestinal peptide-elicited coronary vasodilation in the isolated perfused rat heart." According to recent research from the United States, "The present study investigated the potential role of vasoactive intestinal peptide (VIP) receptors, %VPAC1% and VPAC2, in VIP-elicited coronary vasodilation of the isolated perfused rat heart. Additional studies determined the role of ATP-sensitive (K(ATP)) and voltage-gated K(+) (K(V)) channels in the VIP-elicited coronary vasodilation."

"Both the selective %VPAC1% agonist, K15,R16,L27VIPI-7GRF8-27, and the selective VPAC2 agonist, RO25-1553, decreased coronary vascular resistance (CVR) in a dose-dependent manner, with EC(50) values of 1.67x10(-9)M and 7.11x10(-9)M, respectively (%VPAC1% vs VPAC2 agonist, p<0.05). K15,R16,L27VIP1-7GRF8-27 and RO25-1553 maximally reduced CVR by -42+/-4% and -39+/-6% at 1x10(-8) and 3x10(-8)M, respectively. VIP at 1x10(-10)M decreased CVR by -14+/-2% in the absence (vehicle), by -11+/-3% in the presence of the nonselective VIP receptor %antagonist% VIP10-28 (1x10(-7)M; p>0.05 vs. vehicle) and by only -4+/-2% in the presence of the selective VPAC2 receptor %antagonist% PACAP6-38 (1x10(-7)M; p<0.05 vs. vehicle). In additional studies, VIP at 1x10(-10)M decreased CVR by -22+/-1% in the absence (control) and by only -10+/-2% in the presence of the nonselective K(+) channel blocker tetrabutylammonium (3x10(-4)M; p<0.05 vs. control). VIP reduced CVR by -4+/-1% in the presence of the K(ATP) channel blocker glibenclamide (3x10(-6)M; p<0.05 vs control) and by -28+/-2% in the presence of the K(V) channel blocker 4-aminopyridine (3x10(-4)M; p>0.05 vs control). Thus, selective %VPAC1% and VPAC2 receptor activation in the coronary circulation produces vasodilation and the VIP-elicited coronary vasodilation involves activation of VPAC2 receptors and K(ATP) but not K(V) channels," wrote D.R. Sawmiller and colleagues, University of South Florida, Health Science Center.

The researchers concluded: "In addition, VIP10-28 does not effectively block coronary vascular VIP receptors."

Sawmiller and colleagues published their study in(Mechanisms of vasoactive intestinal peptide-elicited coronary vasodilation in the isolated perfused rat heart. Neuropeptides, 2006;40(5):349-55).

For additional information, contact D.R. Sawmiller, University of South Florida Health Science Center, Dept. of Internal Medicine, Cardiology, Tampa, FL 33612-4799 U.S.

Study 2: Deglycosylated anti-amyloid-beta antibodies eliminate cognitive deficits and reduce parenchymal amyloid with minimal vascular consequences in aged amyloid precursor protein transgenic mice.

Researchers in the United States report, "Systemic administration of anti-amyloid-beta (A-beta) antibodies results in reduced parenchymal amyloid but increased vascular amyloid and microhemorrhage in amyloid precursor protein (APP) transgenic mice. Here, we evaluate the effects of reducing effector interactions of the antibody via deglycosylation. Mice aged 20 months were treated weekly for four months and tested behaviorally before they were killed. APP transgenic mice receiving either anti-A-beta (2H6) or deglycosylated anti-A-beta (de-2H6) showed significant improvement in radial arm water maze performance compared with mice receiving a control antibody," .

"Both groups receiving anti-A-beta antibodies showed significant reductions in total A-beta immunochemistry and Congo red," said Donna M. Wilcock and collaborators at the University of South Florida and Rinat Neurosciences Corporation. "Significantly fewer vascular amyloid deposits and microhemorrhages were observed in mice administered the de-2H6 antibody compared with those receiving unmodified 2H6 antibody."

The scientists concluded, "Deglycosylated anti-A-beta antibodies may be preferable to unmodified IgG because they retain the cognition-enhancing and amyloid-reducing properties of anti-A-beta immunotherapy, while greatly attenuating the increased vascular amyloid deposition and microhemorrhage observed with unmodified IgG."

Wilcock and her coauthors published their study in the (Deglycosylated anti-amyloid-beta antibodies eliminate cognitive deficits and reduce parenchymal amyloid with minimal vascular consequences in aged amyloid precursor protein transgenic mice. J Neurosci, 2006;26(20):5340-5346).

For additional information, contact Dave Morgan, Department of Pharmacology and Molecular Therapeutics, University of South Florida, Alzheimer Research Laboratory, 12901 Bruce B. Downs Boulevard, MDC Box 9, Tampa, FL 33612, USA. dmorgan@hsc.usf.edu.

Study 3: A study from the United States has chronicled the evaluation of toxicity following electrically mediated interleukin-12 (IL-12) gene delivery in a B16 mouse melanoma model.

"IL-12 has potential as an immunotherapeutic agent for the treatment of cancer but is unfortunately associated with toxicity. Delivery of a plasmid encoding IL-12 with electroporation induces an antitumor effect in the B16 mouse melanoma model without serious side effects," wrote L. Heller and colleagues, University of South Florida.

They continued that the study was done "to translate this observation to the clinic, an evaluation of toxicity was done in the mouse model."

"Weight change, tumor response, blood chemistry and hematology values, and serum IL-12 levels were evaluated. Multiple tissues were analyzed histopathologically.

"A pronounced reduction in tumor volume, including a large percentage of complete regressions, was observed after electrically mediated gene therapy. No significant increases in serum IL-12 levels were detected. Tumor-bearing mice showed an increased number of atypical hematology values when compared with normal naive controls," wrote the scientists.

"Statistically significant differences in chemistry and hematology values were observed sporadically in most of the standard chemistry and hematology categories in all groups. The only histopathologic abnormality specific to the animals receiving both plasmid and electroporation was inflammation associated with the kidney at the last time point.

"In general, mice that received both plasmid and electroporation showed the least abnormal histopathologic findings and were found to be in the best health, reflecting the reduced burden of disease," the authors wrote.

They concluded, "No significant toxic effects due to the IL-12 gene therapy were observed."

Heller and colleagues published the results of their research in (Evaluation of toxicity following electrically mediated interleukin-12 gene delivery in a B16 mouse melanoma model. Clin Cancer Res, 2006;12(10):3177-3183).

For additional information, contact L. Heller, University of South Florida, College of Medicine, Department of Medical Microbiology & Immunology, MDC Box 16, 12901 Bruce B Downs Blvd., Tampa, FL 33612, USA.

Keywords: Tampa, Florida, United States, Cancer Gene Delivery, Electric-Mediated Therapy, Interleukin-12, Immunotherapy, Melanoma, Mouse Models.

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2/7/106 (Item 2 from file: 135)
DIALOG(R)File 135:NewsRx Weekly Reports

0000426885 (THIS IS THE FULLTEXT)
Researchers' findings from University of South Florida, U.S., advance research

Science Letter, January 30, 2007, p.1824

DOCUMENT TYPE: Expanded Reporting LANGUAGE: English
RECORD TYPE: FULLTEXT
AUDIENCE: Professional
WORD COUNT: 1111

TEXT: Researchers' findings from University of South Florida, U.S., advance research.

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"Both the selective %VPAC1% agonist, K15,R16,L27VIPI-7GRF8-27, and the selective VPAC2 agonist, RO25-1553, decreased coronary vascular resistance (CVR) in a dose-dependent manner, with EC(50) values of 1.67x10(-9)M and 7.11x10(-9)M, respectively (%VPAC1% vs VPAC2 agonist, p<0.05). K15,R16,L27VIP1-7GRF8-27 and RO25-1553 maximally reduced CVR by -42+/-4% and -39+/-6% at 1x10(-8) and 3x10(-8)M, respectively. VIP at 1x10(-10)M decreased CVR by -14+/-2% in the absence (vehicle), by -11+/-3% in the presence of the nonselective VIP receptor %antagonist% VIP10-28 (1x10(-7)M; p>0.05 vs. vehicle) and by only -4+/-2% in the presence of the selective VPAC2 receptor %antagonist% PACAP6-38 (1x10(-7)M; p<0.05 vs. vehicle). In additional studies, VIP at 1x10(-10)M decreased CVR by -22+/-1% in the absence (control) and by only -10+/-2% in the presence of the nonselective K(+) channel blocker tetrabutylammonium (3x10(-4)M; p<0.05 vs. control). VIP reduced CVR by -4+/-1% in the presence of the K(ATP) channel blocker glibenclamide (3x10(-6)M; p<0.05 vs control) and by -28+/-2% in the presence of the K(V) channel blocker 4-aminopyridine (3x10(-4)M; p>0.05 vs control). Thus, selective %VPAC1% and VPAC2 receptor activation in the coronary circulation produces vasodilation and the VIP-elicited coronary vasodilation involves activation of VPAC2 receptors and K(ATP) but not K(V) channels," wrote D.R. Sawmiller and colleagues, University of South Florida, Health Science Center.

The researchers concluded: "In addition, VIP10-28 does not effectively block coronary vascular VIP receptors."

Sawmiller and colleagues published their study in(Mechanisms of vasoactive intestinal peptide-elicited coronary vasodilation in the isolated perfused rat heart. Neuropeptides, 2006;40(5):349-55).

For additional information, contact D.R. Sawmiller, University of South Florida Health Science Center, Dept. of Internal Medicine, Cardiology, Tampa, FL 33612-4799 U.S.

Study 2: Pharmacological approaches to ameliorating catabolic conditions are reviewed.

"Nutritional debilitation is among the most devastating and life-threatening aspect of various diseases. It arises from a complex interaction between the illness and the host," investigators in the United States report in their review.

E.M. Elamin and colleagues at the University of Southern Florida explained, "This process includes cytokine production, release of lipid-mobilizing and proteolysis-inducing factors, and alterations in intermediary metabolism. As a result, many patients develop cachexia with progressive body fat and muscle tissue wasting with associated worsening of their clinical status and a lower quality of life. In this review, up-to-date information about different approaches to pharmacologic management of cachexia will be addressed."

"Until recently," they continued, "the two major options for pharmacological therapy were either progestational agents or corticosteroids. Knowledge of the mechanisms of cachexia, however, has led to newer therapeutic interventions for treating several aspects of the syndrome. These include antiserotonergic agents, branched-chain amino acids, eicosapentaenoic acid, cannabinoids, melatonin, and thalidomide - all of which act on the feeding-regulatory circuitry to increase appetite and inhibit illness-derived catabolic factors."

The authors finished, "Information from this review will guide health care providers in limiting weight loss and improving performance status of cachectic patients through pharmacological therapy, with the hope that such therapy will extend patients' survival and improve their qualities of life."

Elamin and colleagues published their review in (Pharmacological approaches to ameliorating catabolic conditions. Curr Opin Clin Nutr Metab Care, 2006;9(4):449-454).

For additional information, contact E.M. Elamin, University of Southern Florida, College Medical, 12901 Bruce B Downs Blvd., MDC 59, Tampa, FL 33612, USA.

Study 3: Colorectal cancer patients having undergone a complication-free course of hepatic artery infusional (HAI) chemotherapy were conferred a survival advantage.

"HAI chemotherapy has been shown to favorably impact outcome in patients with metastatic colorectal cancer, but complications often preclude complete treatment. The purpose of this study was to determine whether HAI complications impact survival in these patients," scientists writing in the journal reported.

"Patients undergoing HAI pump placement at our institution from September 2001 to July 2004 were separated into terciles based on the number of treatments completed: less than or equal to1 (none), 2 to 4 (partial), and greater than or equal to5 (complete)," explained D. Osborne and colleagues, University of South Florida. "Complications relating to pump placement or treatment were recorded for each and their impact on survival was determined. Kaplan-Meier survival in 15 patients receiving no treatment was significantly shorter than 7 patients completing therapy (p=.02).

"Thirty-three percent of patients receiving no therapy were alive at 26 months, whereas 63% of partially and 86% of completely treated patients were alive at 32 and 30 months, respectively. Patients receiving no treatment had more overall complications (80%) and significantly (p<.05) more pump-related complications (60%) than those completing therapy (43% and 0%, respectively). Cox regression revealed a significant correlation to gender (hazard ratio, 3.9), tumor size (hazard ratio, 1.17), and carcinoembryonic antigen level (hazard ratio, 1.02) to survival."

The researchers concluded, "Patients receiving complete HAI treatment survive longer than those receiving no treatment. Potentially preventable pump-related complications not only impacted the patients' ability to continue therapy, but survival times as well."

Osborne and colleagues published their study in (A complication-free course ensures a survival advantage in patients after regional therapy for metastatic colorectal cancer. Am Surg, 2006;72(6):505-510).

Additional information can be obtained by contacting E. Zervos, University of South Florida, Tampa General Hospital, POB 1289, Room F145, Tampa, FL 33601, USA.

Keywords: Tampa, Florida, United States, Chemotherapy, Colon Cancer, Colon Carcinoma, Colorectal Cancer, Gastroenterology, Oncology, Rectal Cancer, Rectal Carcinoma, Hepatic Artery Infusional, Survival Advantage.

2/7/107 (Item 3 from file: 135)
DIALOG(R)File 135:NewsRx Weekly Reports

0000408724 (THIS IS THE FULLTEXT)
New findings from Tel-Aviv University describe advances in proteomics
Proteomics Weekly, January 15, 2007, p.244

DOCUMENT TYPE: Expanded Reporting LANGUAGE: English
RECORD TYPE: FULLTEXT
AUDIENCE: Professional
WORD COUNT: 343

TEXT: A new study, "Novel extended and branched N-terminal analogs of VIP," is now available. According to a study from Tel Aviv, Israel, "The

effects of vasoactive intestinal peptide (VIP) are primarily mediated through %VPAC1% and VPAC2, receptors that are preferentially coupled to adenylate cyclase activation. As a large majority of the potent VIP %antagonists% have modifications in the N-terminal domain of the peptide, the effect of multiplication of this domain on VIP was examined with the aim of possibly amplifying peptide-receptor (%VPAC1%) activation.".

"Several VIP analogs were designed and synthesized, each carrying multiplication of the N-terminal domain that was obtained by either linear tandem extension or by parallel branching. Circular dichorism (CD) analysis revealed that these extended/branched peptides maintained an alpha helical structure in organic environment, similar to VIP. A specific branched VIP analog was found to be slightly more potent towards %VPAC1%-related cAMP production as compared to VIP. This analog could have potential therapeutic value in several disorders, similar to VIP. Two branched N-terminal VIP sequences demonstrated superior receptor binding and activation as compared to two N-terminals in tandem. The results suggest that correct alignment of the VIP N-terminal region is important for receptor binding and activation," wrote D. Dangoor and colleagues, Tel-Aviv University.

The researchers concluded: "However, increased receptor binding was not directly associated with increased cAMP production suggesting steric dynamic interactions."

Dangoor and colleagues published the results of their research in Regulatory Peptides (Novel extended and branched N-terminal analogs of VIP. Regulatory Peptides, 2006;137(1-2):42-9).

For additional information, contact D. Dangoor, Sackler School of Medicine, Dept. of Human Molecular Genetics and Biochemistry, Tel Aviv University, Einstein Street, Tel Aviv 69978, Israel.

The publisher of the journal Regulatory Peptides can be contacted at: Elsevier Science BV, PO Box 211, 1000 AE Amsterdam, Netherlands.

Keywords: Israel, Tel Aviv, Peptide, Proteins, Proteomics.

2/7/108 (Item 4 from file: 135)
DIALOG(R)File 135:NewsRx Weekly Reports

0000395541 (THIS IS THE FULLTEXT)
Research reports from Central South University, Department of Physiology provide new insights into proteomics
Anti-Infectives Week, January 1, 2007, p.68

DOCUMENT TYPE: Expanded Reporting LANGUAGE: English
RECORD TYPE: FULLTEXT
AUDIENCE: Professional
WORD COUNT: 355

TEXT: New research, "Vasoactive intestinal peptide enhances wound healing and proliferation of human bronchial epithelial cells," is the subject of a report. According to a study from Changsha, People's Republic of China, "In the present study, we investigated the effects of vasoactive intestinal peptide (VIP) on wound healing of bronchial epithelium. Wound healing of the mechanical damaged human bronchial epithelial cells (HBEC) was observed in the absence or presence of VIP.".

"Effects of VIP on chemotactic migration, cell proliferation of HBEC were also tested. HBEC chemotaxis was assessed by the blind well chamber technique, the cell cycle was determined by flow cytometry, and cell proliferation was determined by measuring the expression of proliferating cell nuclear antigen Ki67. Effects of VIP on epithelial E-cadherins protein and mRNA were also measured by immunohistochemistry and RT-PCR. The results showed that VIP accelerated the recovery of wound area of HBEC. VIP increased the migration and proliferation of HBEC, and these effects were blocked by a %VPAC1% receptor %antagonist%. VIP also increased the expression of E-cadherin mRNA and protein in HBEC, suggesting that protective effects of VIP on wound healing may be related to its ability to increase the expression of E-cadherin," wrote C.X. Guan and colleagues, Central South University, Department of Physiology.

The researchers concluded: "VIP has protective effects against human bronchial epithelial cell damage, and the beneficial effects of VIP might be mediated, at least in part, by %VPAC1%, and associated with increased expression of E-cadherin."

Guan and colleagues published their study in(Vasoactive intestinal peptide enhances wound healing and proliferation of human bronchial epithelial cells. Peptides, 2006;27(12):3107-14).

For more information, contact C.X. Guan, Central South University Xiangya Medical School, Dept. of Physiology, Changsha, Hunan 410078, China.

Publisher contact information for the journal is: Elsevier Science Inc., 360 Park Avenue South, New York, NY 10010-1710, USA.

Keywords: People's Republic of China, Changsha, Anti-Infectives, Gastroenterology, Peptide, Proteins, Proteomics.

2/7/109 (Item 5 from file: 135)
DIALOG(R)File 135:NewsRx Weekly Reports

0000392537 (THIS IS THE FULLTEXT)
Research reports on cell biology from University libre of Bruxelles provide new insights
Science Letter, January 2, 2007, p.197

DOCUMENT TYPE: Expanded Reporting LANGUAGE: English
RECORD TYPE: FULLTEXT
AUDIENCE: Professional
WORD COUNT: 501

TEXT: Scientists discuss in "Asn229 in the third helix of %VPAC1% receptor is essential for receptor activation but not for receptor phosphorylation and internalization: comparison with Asn216 in VPAC2 receptor" new findings in cell biology. According to recent research published in the journal Cellular Signalling , "After stimulation with agonist, G protein coupled receptors (GPCR) undergo conformational changes that allow activation of G proteins to transduce the signal, followed by phosphorylation by kinases and arrestin binding to promote receptor internalization. Actual paradigm, based on a study of GPCR-A/rhodopsin family, suggests that a network of interactions between conserved residues located in transmembrane (TM) domains (mainly TM3, TM6 and TM7) is involved in the molecular switch leading to GPCR activation.".

"We evaluated in CHO cells expressing the VPAC(1) receptor the role of the third transmembrane helix in agonist signalling by point mutation into Ala of the residues highly conserved in the secretin-family of receptors: Y(224), N(229), F(230), W(232), E(236), G(237), Y(239), L(240). N(229)A VPAC(1) mutant was characterized by a decrease in both potency and efficacy of VIP stimulated adenylate cyclase activity, by the absence of agonist stimulated [Ca(2+)](i) increase, by a preserved receptor recognition of agonists and %antagonist% and by a preserved sensitivity to GTP suggesting the importance of that residue for efficient G protein activation. N(229)D mutant was not expressed at the membrane, and the N(229)Q with a conserved mutation was less affected than the A mutant. Agonist stimulated phosphorylation and internalization of N(229)A and N(229)Q VPAC(1) were unaffected. However, the re-expression of internalized mutant receptors, but not that of the wild type receptor, was rapidly reversed after VIP washing. Receptor phosphorylation, internalization and re-expression may be thus dissociated from G protein activation and linked to another active conformation that may influence its trafficking. Mutation of that conserved amino acid in VPAC(2) could be investigated only by a conservative mutation (N(216)Q) and led to a receptor with a low VIP stimulation of adenylate cyclase, receptor phosphorylation and internalization," wrote I. Nachtergael and colleagues, University libre of Bruxelles.

The researchers concluded: "This indicated the importance of the conserved N residue in the TM3 of that family of receptors."

Nachtergael and colleagues published their study in Cellular Signalling (Asn229 in the third helix of %VPAC1% receptor is essential for

receptor activation but not for receptor phosphorylation and internalization: comparison with Asn216 in VPAC2 receptor. Cellular Signalling, 2006;18(12):2121-30).

For additional information, contact I. Nachtergael, Universite Libre de Bruxelles, Dept. of Biological Chemistry and Nutrition, Faculty of Medicine, Belgium.

The publisher's contact information for the journal Cellular Signalling is: Elsevier Science Inc., 360 Park Avenue South, New York, NY 10010-1710, USA.

Keywords: Belgium, Cell Biology, Cellular.

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2/7/110 (Item 6 from file: 135)
DIALOG(R)File 135:NewsRx Weekly Reports

0000389917 (THIS IS THE FULLTEXT)
Studies from University of South Florida, Health Science Center have provided new information about proteomics
Gastroenterology Week, December 25, 2006, p.326

DOCUMENT TYPE: Expanded Reporting LANGUAGE: English
RECORD TYPE: FULLTEXT
AUDIENCE: Professional
WORD COUNT: 474

TEXT: Fresh data on proteomics are presented in the report "Mechanisms of vasoactive intestinal peptide-elicited coronary vasodilation in the isolated perfused rat heart." According to recent research from the United States, "The present study investigated the potential role of vasoactive intestinal peptide (VIP) receptors, %VPAC1% and VPAC2, in VIP-elicited coronary vasodilation of the isolated perfused rat heart. Additional studies determined the role of ATP-sensitive (K(ATP)) and voltage-gated K(+) (K(V)) channels in the VIP-elicited coronary vasodilation.".

"Both the selective %VPAC1% agonist, K15,R16,L27VIPI-7GRF8-27, and the selective VPAC2 agonist, RO25-1553, decreased coronary vascular resistance (CVR) in a dose-dependent manner, with EC(50) values of 1.67x10(-9)M and 7.11x10(-9)M, respectively (%VPAC1% vs VPAC2 agonist, p<0.05). K15,R16,L27VIP1-7GRF8-27 and RO25-1553 maximally reduced CVR by -42+/-4% and -39+/-6% at 1x10(-8) and 3x10(-8)M, respectively. VIP at 1x10(-10)M decreased CVR by -14+/-2% in the absence (vehicle), by -11+/-3% in the presence of the nonselective VIP receptor %antagonist% VIP10-28 (1x10(-7)M; p>0.05 vs. vehicle) and by only -4+/-2% in the presence of the selective VPAC2 receptor %antagonist% PACAP6-38 (1x10(-7)M; p<0.05 vs. vehicle). In additional studies, VIP at 1x10(-10)M decreased CVR by -22+/-1% in the absence (control) and by only -10+/-2% in the presence of the nonselective K(+) channel blocker tetrabutylammonium (3x10(-4)M; p<0.05 vs. control). VIP reduced CVR by -4+/-1% in the presence of the K(ATP) channel blocker glibenclamide (3x10(-6)M; p<0.05 vs control) and by -28+/-2% in the presence of the K(V) channel blocker 4-aminopyridine (3x10(-4)M; p>0.05 vs control). Thus, selective %VPAC1% and VPAC2 receptor activation in the coronary circulation produces vasodilation and the VIP-elicited coronary vasodilation involves activation of VPAC2 receptors and K(ATP) but not K(V) channels," wrote D.R. Sawmiller and colleagues, University of South Florida, Health Science Center.

The researchers concluded: "In addition, VIP10-28 does not effectively block coronary vascular VIP receptors."

Sawmiller and colleagues published their study in Neuropeptides (Mechanisms of vasoactive intestinal peptide-elicited coronary vasodilation in the isolated perfused rat heart. Neuropeptides, 2006;40(5):349-55).

For additional information, contact D.R. Sawmiller, University of South Florida Health Science Center, Dept. of Internal Medicine, Cardiology, Tampa, FL 33612-4799 U.S.

Publisher contact information for the journal Neuropeptides is: Churchill Livingstone, Journal Production Dept., Robert Stevenson House, 1-3 Baxters Place, Leith Walk, Edinburgh EH1 3AF, Midlothian, Scotland.

Keywords: United States, Tampa, Gastroenterology, Neuropeptides, Peptide, Proteins, Proteomics.

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2/7/111 (Item 7 from file: 135)
DIALOG(R)File 135:NewsRx Weekly Reports

0000384255 (THIS IS THE FULLTEXT)
Investigators at Tel-Aviv University zero in on proteomics
Proteomics Weekly, December 18, 2006, p.193

DOCUMENT TYPE: Expanded Reporting LANGUAGE: English
RECORD TYPE: FULLTEXT
AUDIENCE: Professional
WORD COUNT: 315

TEXT: Research findings, "VIP provides cellular protection through a specific splice variant of the PACAP receptor: a new neuroprotection target," are discussed in a new report. "Vasoactive intestinal peptide (VIP) was known to provide neuroprotection. Three VIP receptors have been cloned: %VPAC1%, VPAC2 and PAC1," researchers in Tel Aviv, Israel report.

"A specific splice variant of PAC1 in the third cytoplasmatic loop, hop2, was implicated in VIP-related neuroprotection. We aimed to clone the hop2 splice variant, examine its affinity to VIP and investigate whether it mediates the VIP-related neuroprotective activity. The PAC1 cDNA was cloned from rat cerebral astrocytes. Using genetic manipulation the hop2 splice variant was obtained, then inserted into an expression vector and transfected into COS-7 cells that were used for binding assays. showed that VIP bound the cloned hop2 splice variant. Stearyl-neurotensin(6-11) VIP(7-28) (SNH), an %antagonist% for VIP, was also found to bind hop2. In addition, VIP protected COS-7 cells expressing hop2 from oxidative stress. Parallel assays demonstrated that VIP increased cAMP accumulation in COS-7 cells expressing hop2," wrote I. Pilzer and colleagues, Tel-Aviv University.

The researchers concluded: "These results support the hypothesis that hop2 mediates the cytoprotective effects attributed to VIP."

Pilzer and colleagues published their study in Peptides (VIP provides cellular protection through a specific splice variant of the PACAP receptor: a new neuroprotection target. Peptides, 2006;27(11):2867-76).

For additional information, contact I. Pilzer, Sackler Faculty of Medicine, Dept. of Human Molecular Genetics and Biochemistry, Tel Aviv University, Tel Aviv 69978, Israel.

Publisher contact information for the journal Peptides is: Elsevier Science Inc., 360 Park Avenue South, New York, NY 10010-1710, USA.

Keywords: Israel, Tel Aviv, Peptide, Proteins, Proteomics.

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2/7/112 (Item 8 from file: 135)
DIALOG(R)File 135:NewsRx Weekly Reports

0000233348 (THIS IS THE FULLTEXT)
VIP and PACAP are candidates for multitarget septic shock therapy
Anti-Infectives Week, August 1, 2005, p.5

DOCUMENT TYPE: Editor's Choice LANGUAGE: English
RECORD TYPE: FULLTEXT
AUDIENCE: Professional
WORD COUNT: 438

TEXT: Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activing polypeptide (PACAP) are candidates for multitarget septic

shock therapy.

According to a study from Spain, "Infections caused by Gram-negative bacteria constitute one of the major causes of septic shock, which results from the inability of the immune system to limit bacterial spread during the ongoing infection. In the last decade, it has been demonstrated that vasoactive intestinal peptide and pituitary adenylate cyclase-activing polypeptide are two endogenous immunopeptides, which together with three G protein-coupled receptors (%VPAC1%, VPAC2, and PAC1) exert a significant, therapeutic effect attenuating the deleterious consequences of septic shock by balancing pro- and anti-inflammatory factors.".

"We have recently shown PAC1 receptor involvement in vivo as an anti-inflammatory receptor, at least in part, by attenuating lipopolysaccharide-induced production of pro-inflammatory interleukin-6. The present study deepens in the protective role of PAC1 receptor in septic shock, elucidating its involvement in the modulation of neutrophil recruitment and in the expression of different molecular sensors such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1, fibrinogen, serum amyloid A, and nitric oxide as important, systemic players of the development of septic shock," wrote C. Martinez and colleagues, Complutense University, Madrid.

The researchers continued: "Our results, using ... mice deficient in PAC1 and a PAC1 %antagonist%, show that VIP and PACAP as well as the PAC1 receptor are involved in neutrophil recruitment in different target organs, in adhesion molecules expression, and in coagulation-related molecule fibrinogen synthesis."

The researchers concluded: "Thus, this study provides some important insights with respect to the involvement of PAC1 into the complexities of sepsis and represents an advantage for the design of more specific drugs complementing standard intensive care therapy in severe sepsis, confirming VIP and PACAP as candidates for multitarget therapy of septic shock."

Martinez and colleagues published the results of their research in the Journal of Leukocyte Biology (Analysis of the role of the PAC1 receptor in neutrophil recruitment, acute-phase response, and nitric oxide production in septic shock. J Leukoc Biol, 2005;77(5):729-738).

For additional information, contact C. Martinez, University of Complutense, Madrid, Faculty Med, Dept. Cell Biology, E-28040 Madrid, Spain.

The publisher of the Journal of Leukocyte Biology can be contacted at: Federation American Society Experimental Biology, 9650 Rockville Pike, Bethesda, MD 20814-3998, USA.

Keywords: Madrid, Spain, Bacteriology, Critical Care Medicine, Drugs, Endotoxin, Immunology, Immunopeptides, Inflammation, Nitric Oxide, Sepsis, Septic Shock, Septicemia, Therapy.

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2/7/113 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal

16970448 PASCAL No.: 05-0030495
Ac His SUP 1 (D-Phe SUP 2 , K SUP 1 SUP 5 , R SUP 1 SUP 6 , L SUP 2 SUP 7) VIP (3-7)/GRF (8-27) - a VPAC SUB 1 receptor %antagonist%: is an inverse agonist on two constitutively active truncated VPAC SUB 1 receptors
VERTONGEN Pascale; LANGLET Christelle; LANGER Ingrid; GASPARD Nathalie; ROBBERECHT Patrick
Department of Biochemistry and Nutrition, School of Medicine, Universite Libre de Bruxelles, Bat G/E, CP 611, 808, Route de Lennik, 1070 Bruxelles, Belgium
Journal: Peptides : (New York, NY. 1980), 2004, 25 (11) 1943-1949
ISSN: 0196-9781 CODEN: PPTDD5 Availability: INIST-19060; 354000120552900140
No. of Refs.: 26 ref.
Document Type: P (Serial) ; A (Analytic)
Country of Publication: United States
Language: English
C-terminally truncated human VPAC SUB 1 receptors were constructed and stably transfected in Chinese hamster ovary (CHO) cells. Selected clones expressing comparable receptor densities were studied for ligand's binding properties, basal and stimulated adenylate cyclase activity. The wild-type (1-457) receptor served as reference. The binding properties of all the constructions were preserved. As judged by the intrinsic activity of the partial agonist Q SUP 3 -VIP, the shortest receptors have a moderate impairment of the coupling efficacy to G SUB alpha SUB S protein. Cells expressing the VPAC SUB 1 (1-436) and (1-441) truncated receptors had a two- to three-fold higher basal adenylate cyclase activity than those expressing the wild-type or the VPAC SUB 1 (1-444), (1-433), (1-429), (1-421) and (1-398) receptor. The stimulatory effect of VIP and other agonist was preserved. This suggested that VPAC SUB 1 (1-436) and (1-441) receptors had a constitutive activity. The selective VPAC SUB 1 receptor %antagonist% Ac His SUP 1 (D-Phe SUP 2 , K SUP 1 SUP 5 , R SUP 1 SUP 6 , L SUP 2 SUP 7) VIP (3-7)/GRF (8-27) reduced by 60% the basal activity with an EC SUB 5 SUB 0 value of 3 nM comparable to its IC SUB 5 SUB 0 value for binding. This agonist behaved thus like an inverse agonist on the constitutively active VPAC SUB 1 receptors generated by C-terminal truncation and expressed in CHO cells.

2/7/114 (Item 2 from file: 144)
DIALOG(R)File 144:Pascal

16019269 PASCAL No.: 03-0165787
Immunoeffector and immunoregulatory activities of vasoactive intestinal peptide
5th international meeting: VIP, PACAP, Secretin, Glucagon and Related peptides, November 4-8, 2001, Santa Barbara, California, USA
VOICE Julia K; DORSAM Glenn; CHAN Robert C; GRINNINGER Carola; KONG Yvonne; GOETZL Edward J
PISEGNA Joseph R, ed; WASCHEK James A, ed; SAID Sami I, ed
Departments of Medicine and Immunology, University of California, San Francisco, CA 94143, United States
CURE: Digestive Diseases Research Center, VA Greater Los Angeles Healthcare System, University of California, Los Angeles, CA 90073, United States; Department of Psychiatry, Mental Retardation Research Center, School of Medicine, University of California at Los Angeles, Room 68-225 NPI, 760 Westwood Plaza, Los Angeles, CA 90024-1759, United States; V.A. Medical Center, NY & SUNY Health Sciences Center, Northport, Stony Brook, NY 11794-8172, United States
International Meeting: VIP, PACAP, Secretin, Glucagon and Related Peptides, 5 (Santa Barbara, CA USA) 2001-11-04
Journal: Regulatory peptides, 2002, 109 (1-3) 199-208
ISSN: 0167-0115 CODEN: REPPDY Availability: INIST-18854; 354000106633270270
No. of Refs.: 45 ref.
Document Type: P (Serial); C (Conference Proceedings) ; A (Analytic)
Country of Publication: Netherlands
Language: English
Vasoactive intestinal peptide (VIP) and its two G protein-coupled receptors, VPAC1R and VPAC2R, are prominent in the immune system and potently affect T cells and macrophages. VPAC) Rs are expressed constitutively by blood and tissue T cells, with an order of prevalence of Th2>Thl Ts, and transmit signals suppressive for migration, proliferation and cytokine production. Immune activation of T cells downregulates VPACIRs and upregulates VPAC2Rs. VPAC2Rs mediate T cell chemotaxis, stimulation of some Th2-type cytokines, and inhibition of some Th1-type cytokines. A tentative hypothesis that the VIP-VPAC2R axis is the major neuroregulator of Th2/Thl balance has been confirmed by finding an increased ratio in CD4 T cells of transgenic (TG) mice, expressing high levels of VPAC2Rs, and a decreased ratio in CD4 T cells of VPAC2R-null (K/O) mice. VPAC2R TG mice exhibit an allergic phenotype, whereas the K/O mice are hypoallergic and have heightened delayed-type hypersensitivity. The mechanisms of VIP-VPAC2R effects include decreased Th2 apoptosis, increased Th2-type cytokine production, and greater generation of Th2 memory cells. VPAC2R %antagonists% are being developed to alleviate allergic diseases and

strengthen effector Th1 cell-mediated immunoprotection.

2/7/115 (Item 3 from file: 144)
DIALOG(R)File 144:Pascal

15745540 PASCAL No.: 02-0457256
Expression and function of vasoactive intestinal peptide, pituitary adenylate cyclase-activating polypeptide, and their receptors in the human adrenal gland : The impact of the human genome on endocrinology: Special features
MAZZOCCHI G; MALENDOWICZ L K; REBUFFAT P; GOTTARDO L; NUSSDORFER Gastone G
Department of Human Anatomy and Physiology, Section of Anatomy, University of Padua, 35121 Padua, Italy
Journal: The Journal of clinical endocrinology and metabolism, 2002, 87 (6) 2575-2580
ISSN: 0021-972X CODEN: JCEMAZ Availability: INIST-6022; 354000108372100240
No. of Refs.: 52 ref.
Document Type: P (Serial) ; A (Analytic)
Country of Publication: United States
Language: English
VIP and pituitary adenylate cyclase-activating polypeptide (PACAP) are two regulatory peptides that possess remarkable amino acid sequence homology and act through common receptors, named PAC SUB 1 , VPAC SUB 1 , and VPAC SUB 2 . PAC SUB 1 receptor is selective for PACAP, whereas VPAC SUB 1 and VPAC SUB 2 receptors bind both VIP and PACAP. We have investigated the expression and function of VIP, PACAP, and their receptors in the zona glomerulosa (ZG), zonae fasciculata and reticularis, and adrenal medulla (AM) of the human adrenal cortex. RT-PCR and RIA detected VIP and PACAP expression exclusively in AM cells. RT-PCR demonstrated the presence of PAC SUB 1 mRNA only in AM and of VPAC SUB 1 and VPAC SUB 2 mRNAs in both ZG and AM cells. VIP and PACAP concentration-dependently increased aldosterone and catecholamine secretion from cultured ZG and AM cells. The catecholamine response to both peptides was higher than the aldosterone response, and the secretagogue action of PACAP was more intense than that of VIP. The aldosterone response of cultured ZG cells to VIP or PACAP was unaffected by the PAC SUB 1 receptor %antagonist% PACAP-(6-38) (PAC SUB 1 -A), but was significantly decreased by the VPAC SUB 1 receptor %antagonist% (Ac-His SUP 1 ,D-Phe SUP 2 ,Lys SUP 1 SUP 5 ,Arg SUP 1 SUP 6)VIP-(3-7),GH-releasing factor-(8-27)-NH SUB 2 (VPAC SUB 1 -A). The catecholamine response of cultured AM cells to VIP was lowered by VPAC SUB 1 -A and unaffected by PAC SUB 1 -A; conversely, the catecholamine response to PACAP was reduced by both PAC,-A and VPAC SUB 1 -A. Simultaneous exposure to both %antagonists% did not abolish the catecholamine response to PACAP. Collectively, our findings allow us to conclude that in human adrenals 1) VIP and PACAP biosynthesis exclusively occurs in AM cells; 2) ZG cells are provided with functional VPAC SUB 1 and VPAC SUB 2 receptors, whose activation by VIP or PACAP elicits a moderate aldosterone response; 3) AM cells possess PAC SUB 1 , VPAC SUB 1 , and VPAC SUB 2 receptors, whose activation evokes a marked catecholamine response; and 4) the catecholamine response to PACAP is more intense than that to VIP, because it is mediated by all subtypes of VIP/PACAP receptors.

2/7/116 (Item 4 from file: 144)
DIALOG(R)File 144:Pascal

15380975 PASCAL No.: 02-0069368
Role of endogenous PACAP in catecholamine secretion from the rat adrenal gland
FUKUSHIMA Yasuo; HIKICHI Hirohiko; MIZUKAMI Kazuhiko; NAGAYAMA Takahiro; YOSHIDA Makoto; SUZUKI-KUSABA Mizue; HISA Hiroaki; KIMURA Tomohiko; SATOH Susumu
Laboratory of Pharmacology, Graduate School of Pharmaceutical Sciences, Tohoku University, Aobayama, Sendai 980-8578, Japan; Department of Dental Pharmacology, The Nippon Dental University School of Dentistry at Niigata, Hamaura-cho, Niigata 951-8580, Japan
Journal: American journal of physiology. Regulatory, integrative and comparative physiology, 2001, 50 (5) R1562-R1567
ISSN: 0363-6119 CODEN: AJPRDO Availability: INIST-670E; 354000099277330240
No. of Refs.: 29 ref.
Document Type: P (Serial) ; A (Analytic)
Country of Publication: United States
Language: English
We elucidated the contribution of endogenous pituitary adenylate cyclase-activating polypeptide (PACAP) to neurally evoked catecholamine secretion from the isolated perfused rat adrenal gland. Infusion of PACAP (100 nM) increased adrenal epinephrine and norepinephrine output. The PACAP-induced catecholamine output responses were inhibited by the PACAP type I receptor %antagonist% PACAP(6-38) (30-3,000 nM) but were resistant to the PACAP type II receptor %antagonist% (Lys SUP 1 ,Pro SUP 2 SUP , SUP 5 ,Ara SUP 3 SUP , SUP 4 ,Tyr SUP 6)-vasoactive intestinal peptide (LPAT-VIP; 30-3,000 nM). Transmural electrical stimulation (ES; 1-10 Hz) or infusion of ACh (6-200 nM) increased adrenal epinephrine and norepinephrine output. PACAP-(6-38) (3,000 nM), but not LPAT-VIP, also inhibited the ES-induced catecholamine output responses. However, PACAP-(6-38) did not affect the ACh-induced catecholamine output responses. PACAP at low concentrations (0.3-3 nM), which had no influence on catecholamine output, enhanced the ACh-induced catecholamine output responses, but not the ES-induced catecholamine output responses. These results suggest that PACAP is released from the nerve endings to facilitate the neurally evoked catecholamine secretion through PACAP type I receptors in the rat adrenal gland.

2/7/117 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0295453 DBR Accession No.: 2002-17300 PATENT
Identifying candidate compounds for regulating skeletal muscle mass or function by contacting test compound with vasoactive intestinal peptide receptors or cell expressing the receptor - skeletal muscle mass regulation, vasoactive intestinal peptide receptor and transgenic animal for disease therapy and drug screening
AUTHOR: ISFORT R J; SHELDON R J
PATENT ASSIGNEE: PROCTER and GAMBLE CO 2002
PATENT NUMBER: WO 200235240 PATENT DATE: 20020502 WPI ACCESSION NO.: 2002-471451 (200250)
PRIORITY APPLIC. NO.: US 694519 APPLIC. DATE: 20001023
NATIONAL APPLIC. NO.: WO 2001US43882 APPLIC. DATE: 20011022
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - Identifying (M1) candidate compounds (CC) for regulating skeletal muscle mass or function involves contacting a test compound (TC) with a vasoactive intestinal peptide receptors (VPAC) or cell expressing VPAC receptor and determining whether TC binds to VPAC receptor or TC that activates the VPAC receptors, where the TC that binds to or activates VPAC is identified as CC. DETAILED DESCRIPTION - Identifying (M1) candidate compounds (CC) for regulating skeletal muscle mass or function involves contacting a test compound (TC) with a vasoactive intestinal peptide receptors (VPAC) or a cell expressing a VPAC receptor, preferably VPAC receptor is expressed on a eukaryotic cell and is functional %VPAC1% receptor or VPAC2 receptor and determining whether TC binds to the VPAC receptor, where TC that bind to the VPAC receptor or activate the VPAC receptor are identified as CC for regulating skeletal muscle mass or function. Identified CC may be administered to a non-human animal and those CC that regulate skeletal muscle mass or function in the animal are identified as candidate therapeutic compounds for regulating skeletal

muscle mass or function in vivo or INDEPENDENT CLAIMS are also included for the following: (1) identifying (M2) candidate therapeutic compounds for regulating skeletal muscle mass or function by contacting a TC with a cell which expresses a functional VPAC receptor, determining whether TC activates the VPAC receptor and administering TC determined to a non-human animal to activate the VPAC receptor, and determining whether TC regulates skeletal muscle mass or function in the animal, where TC regulate skeletal muscle mass or function in the animal in vivo; (2) identifying (M3) CC that prolong or augment the activation of a VPAC receptor signal transduction pathway, by contacting a TC with a cell which expresses a functional VPAC receptor, treating the cell with an agonist for a sufficient time and at a sufficient concentration to cause desensitization of the VPAC receptors in control cells, and determining the level of activation of the VPAC receptor, where TC that prolong or augment the activation of a VPAC receptor or of a VPAC receptor signal transduction pathway are identified as CC for regulating skeletal muscle mass or function; (3) identifying (M4) CC for increasing VPAC receptor expression, by contacting a TC with a cell or cell lysate containing a receptor gene operatively associated with a VPAC receptor regulatory element, and detecting expression of the reporter gene where TC that increase expression of the reporter gene are identified as CC for regulating skeletal muscle mass or function; (4) identifying (M5) CC for increasing the expression of vasoactive intestinal peptide (VIP) or a VIP analog, by contacting a TC with a cell or cell lysate containing a reporter gene operatively associated with a VIP analog regulatory element, and detecting expression of the reporter gene where TC that increase expression of the reporter gene are identified as compound for regulating skeletal muscle mass or function; (5) a pharmaceutical composition (PC), comprises a safe and effective amount of a VPAC receptor agonist; (6) increasing (M6) skeletal muscle mass or function in a subject in which such an increase is desirable, by identifying a subject in which an increase in muscle mass or function desirable, and administering to the subject a safe and effective amount of compound selected from the group consisting of a VPAC receptor agonist, a compound that prolongs or augments the activation of VPAC receptors or the activation of a VPAC receptor signal transduction pathway, an expression vector encoding a functional VPAC receptor, an expression vector encoding a constitutively active VPAC receptor, an expression vector encoding a constitutively active VPAC receptor, a compound that increases expression of VPAC receptors, a compound that increases expression of VIP and a compound that increases expression of a VIP analog; (7) treating (M7) skeletal muscle atrophy in a subject in need of such treatment, by identifying a subject in need of treatment for skeletal muscle atrophy; and (8) a purified antibody (Ab) specific for a VPAC receptor, where the antibody is a chimeric or human antibody, preferably human. BIOTECHNOLOGY - Preferred Method: In M1, the cell having a cellular cAMP level, TC activates the VPAC receptor by measuring the cellular cAMP level. The cell further comprises a reporter gene operatively associated with a cAMP responsive element and measuring the cellular cAMP level involves measuring expression of the reporter gene, preferably the reporter gene is alkaline phosphatase, chloramphenicol acetyltransferase, luciferase, glucuronide synthetase, growth hormone, placental alkaline phosphatase or green fluorescent protein. In M7 and M8, the VPAC receptor agonist is VIP, PACAP-27, PACAP-38, helodermin, peptide histidine isoleucine amide, peptide histidine methionine amide, peptide histidine valine amide, growth hormone releasing hormone, secretin, glucagon, (Arg15, Arg21) VIP, (Arg15,20,21Leu17)-VIP-Gly-Lys-Arg-NH2, (K15, R16, L27, VIP(1-7), GRF(8-27)-NH2), multimeric VIP fusion protein, Ro 25-1553, Ro 25-1392 or PACAP (6-38). Preferred Antibody: Ab is an agonist of VPAC receptor. ACTIVITY - Antibacterial; immunosuppressive; cytostatic; immunomodulator; antiinflammatory. MECHANISM OF ACTION - Regulator of skeletal muscle mass or function. A human male subject weighing 50 kg and had significant muscular atrophy of the arms and legs due to prolonged bed rest, was treated to reverse the skeletal muscle atrophy. Once each week for a period of 3 months, 15 ml of an aqueous solution of pH 6 comprising the anti-VPAC2 receptor was administered to the subject via intravenous injection. The solution comprises 20 mg/ml VPAC2 receptor agonist antibody, 0.47 mg/ml L-histidine HCl, 0.3 mg/ml L-histidine, 20 mg/ml alpha,alpha-trehalose dihydrate, 0.1 polysorbate 20, and bacteriostatic sterile water. At the end of the treatment period, the subject exhibited measurable increase of muscle mass, strength and mobility of the arms and legs. USE - M1 is useful for identifying CC for regulating skeletal mass or function. M3 is useful for identifying CC that prolong or augment the activation of VPAC receptor or VPAC receptor signal transduction pathway. M4 is useful for identifying CC for increasing VPAC receptor expression and M5 is useful for identifying CC for increasing the expression of VIP or a VIP analog. M7 is useful for increasing skeletal mass or function in a subject and M8 is useful for treating skeletal muscle atrophy in a subject (claimed). PC is useful for modulating skeletal muscle atrophy which includes skeletal muscle atrophy induced by disuse due to surgery, bed rest, broken bones, denervation/nerve damage due to spinal cord injury, autoimmune disease, infectious disease, glucocorticoid use for unrelated conditions, sepsis due to infection or other causes, nutrient limitation due to illness or starvation, cancer cachexia, chronic inflammation, AIDS cachexia, COPD, congestive heart failure, sarcopenia and genetic disorders, e.g., muscular dystrophies, neurodegenerative diseases.ADMINISTRATION - PC is administered by intranasal, transdermal, inhalation, parenteral, cutaneous, oral or rectal route. No dosage details is given. (87 pages)

2/7/118 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

143311956 CA: 143(17)311956u PATENT
VPAC1-selective antagonists and their pharmacological methods of use
INVENTOR(AUTHOR): Pan, Clark; Roczniak, Steve
LOCATION: USA
ASSIGNEE: Bayer Pharmaceuticals Corp.
PATENT: U.S. Pat. Appl. Publ. ; US 20050203009 A1 DATE: 20050915
APPLICATION: US 2004799897 (20040312)
PAGES: 17 pp. CODEN: USXXCO LANGUAGE: English
PATENT CLASSIFICATIONS:
CLASS: 514012000; A61K-038/17A; C07K-014/71B; C07H-021/04B; C12N-015/09B
SECTION:
CA263006 Pharmaceuticals
CA202XXX Mammalian Hormones
IDENTIFIERS: VPAC1 antagonist peptide sequence
DESCRIPTORS:
Animal cell line...
H727; VPAC1-selective antagonists and their pharmacol. methods of use
Pituitary adenylate cyclase-activating polypeptide receptor...
type II; VPAC1-selective antagonists and their pharmacol. methods of use
Pituitary adenylate cyclase-activating polypeptide receptor...
type III; VPAC1-selective antagonists and their pharmacol. methods of use
VIP receptors...
VIP1; VPAC1-selective antagonists and their pharmacol. methods of use
VIP receptors...
VIP2; VPAC1-selective antagonists and their pharmacol. methods of use
Polyoxyalkylenes,biological studies... Peptides,biological studies...
Protein sequences... Cell proliferation... Human...
VPAC1-selective antagonists and their pharmacol. methods of use
CAS REGISTRY NUMBERS:
60-92-4 formation of; VPAC1-selective antagonists and their pharmacol. methods of use
443681-66-1 86168-78-7 127317-03-7 864679-61-8 864679-62-9 864679-63-0 37221-79-7 25322-68-3 25322-69-4 9034-39-3 129069-75-6
VPAC1-selective antagonists and their pharmacol. methods of use

2/7/119 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

136396213 CA: 136(26)396213c JOURNAL
(N-stearyl,Norleucine17)VIP hybrid is a broad spectrum vasoactive intestinal peptide receptor antagonist
AUTHOR(S): Moody, Terry W.; Jensen, Robert T.; Fridkin, Mati; Gozes, Illana
LOCATION: Medicine Branch, National Cancer Institute, Rockville, MD, 20850, USA
JOURNAL: J. Mol. Neurosci. DATE: 2002 VOLUME: 18 NUMBER: 1/2 PAGES: 29-35 CODEN: JMNEES ISSN: 0895-8696 LANGUAGE: English PUBLISHER: Humana Press Inc.
SECTION:
CA202006 Mammalian Hormones
IDENTIFIERS: stearyl norleucyl VIP hybrid VPAC1 VPAC2 PAC1 receptor antagonist, PACAP receptor antagonist stearyl norleucyl VIP hybrid
DESCRIPTORS:
Animal cell line...
CHO; (N-stearyl,Nle17)VIP hybrid is broad spectrum VIP receptor antagonist
Pituitary adenylate cyclase-activating polypeptide receptor...
type I; (N-stearyl,Nle17)VIP hybrid is broad spectrum VIP receptor antagonist
Pituitary adenylate cyclase-activating polypeptide receptor...
type II; (N-stearyl,Nle17)VIP hybrid is broad spectrum VIP receptor antagonist
Pituitary adenylate cyclase-activating polypeptide receptor...
type III; (N-stearyl,Nle17)VIP hybrid is broad spectrum VIP receptor antagonist
VIP receptors...
VIP1; (N-stearyl,Nle17)VIP hybrid is broad spectrum VIP receptor antagonist
VIP receptors...
VIP2; (N-stearyl,Nle17)VIP hybrid is broad spectrum VIP receptor antagonist
Animal cell line...
3T3; (N-stearyl,Nle17)VIP hybrid is broad spectrum VIP receptor antagonist
CAS REGISTRY NUMBERS:
60-92-4 37221-79-7 129069-75-6 149673-59-6 (N-stearyl,Nle17)VIP hybrid is broad spectrum VIP receptor antagonist
27feb07 13:52:32 User219511 Session D677.4